

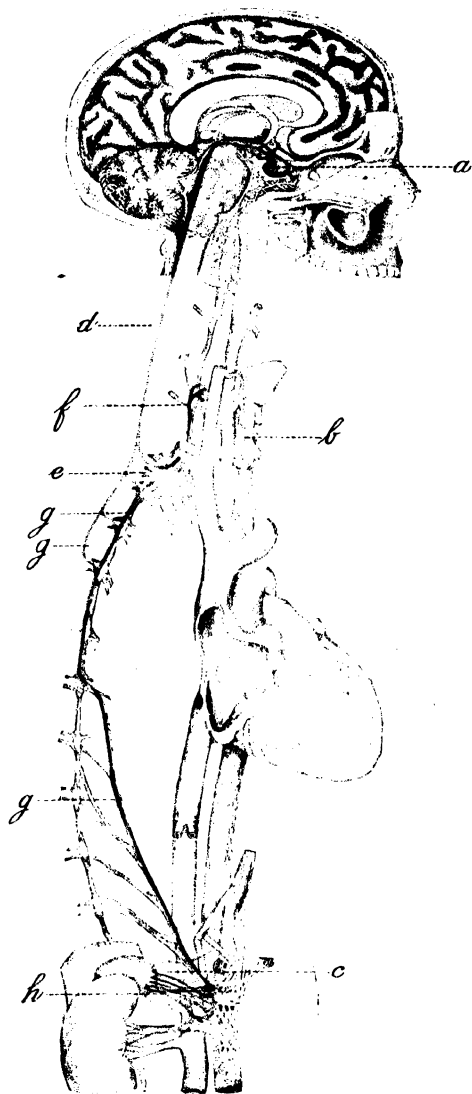
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THE INNERVATION OF THE ADRENAL SYSTEM. [Gajous.]

a, Pituitary body containing adreno-thyroid center. b, Thyroid gland, supplied by nerves e, f, derived from the pituitary. c, Adrenal gland. d, Cervical cord. e, f, Nerves derived from pituitary body via the medulla. g, g, Splanchnic nerves. h, Adrenal gland.

THE INTERNAL SECRETIONS

AND THE

PRINCIPLES OF MEDICINE

BY

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VOLUME FIRST

WITH FORTY-FIVE ILLUSTRATIONS

SIXTH EDITION



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PREFACE TO THE FIFTH AND SIXTH EDITIONS.

WHEN the first edition of this work appeared (1903), the author hardly expected that his views, submitted only with the intention of opening new fields of investigation, would, within comparatively few years, be granted an enviable position in the practical field. He can only ascribe the large patronage that the work has received from the general profession to the admittedly better results obtained in practice by the adoption of the newer principles it has introduced. Besides taking into account the functions of important organs—the ductless glands—in every morbid process treated, the author has tried to emphasize the value of close analysis in the treatment of disease and to cultivate a distaste for the empiricism which attends the present use of remedies. It is unquestionably because such an effort meets a corresponding desire in the profession at large that so encouraging a response has been vouchsafed.

The last three editions extended greatly, as compared to former ones, the scope of the work in the practical field. About 400 pages of the first volume, devoted heretofore to a study of the functions of the adrenals and thyroid, were deemed no longer necessary to introduce the author's views, and were replaced by a corresponding number of pages in which questions of paramount importance to the practitioner were considered. The fifth and sixth editions served mainly to bring the various subjects to date, and to amplify some of them—the chapter on *Organotherapy* for example.

The first two chapters are devoted to the connection of the adrenals with the lethal trend of many infections and intoxications. It is shown therein that many diseases prove fatal through the fact that inhibition or destruction of the functions of the adrenals as a cause of death is at present overlooked. As the diseases which unquestionably implicate so seriously these organs include practically all febrile intoxications and infections, especially those of childhood, the importance of the subject as a whole can hardly be sufficiently emphasized.

The next three chapters, also composed entirely of new matter, cover a similar field, in so far as the thyroid and parathyroids are concerned, besides analyzing from a new standpoint the diseases due to these organs: myxœdema, cretinism, infantilism, etc. These prominent syndromes are rarely met with, however, as compared with the less clearly identified manifestations of thyroparathyroid insufficiency, treated in the present work under the caption of hypothyroidia. Many disorders grouped under the terms "rheumatism," "neurasthenia," "autointoxications," "gout," which thwart the physicians' efforts, are but manifestations of this condition. This applies also to a large proportion of mentally defective, obese, and imperfectly developed subjects, all of whom, particularly children, may be greatly benefited when their true condition is recognized.

The twelfth chapter has been devoted to **organotherapy**. The author is not of the opinion that "internal secretions" are as numerous in the body as is generally believed; an effort is made, therefore, to identify those which merit this designation, and also the active factor in each of the organic products that have been found of value in various diseases. This also has for its purpose to counteract, as much as possible, the prevailing empirical use of these agents, several of which, intelligently employed, are of great therapeutic efficiency.

The balance of the work has been carefully revised, and where needed, as in the eleventh chapter, considerably amplified. This applies also to the second volume, but only in so far as needed corrections were concerned.

The author may add that he has also received encouragement from the fact that his views are steadily gaining ground, even in the experimental field, as will be seen by a perusal of the work.

C. E. DE M. SAJOUS.

2043 WALNUT STREET,
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Fifth Edition, April 1, 1912.

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PREFACE TO THE SECOND AND THIRD EDITIONS.

(Containing a summary of the author's newer
conceptions up to 1907.)

WHILE the manuscript for the first volume was delivered to the publishers in 1902, the second volume was only finished in 1907. As the latter embodied researches carried on during the interval of five years between the two volumes, it became necessary to correct what errors the first contained in the light of these researches. This feature, coupled with the large patronage the medical profession has granted the work, has imposed the need of new editions. That very few corrections have proven necessary, either by reason of these investigations or of what justified criticisms the work has received, is shown by the list of additions to our knowledge (see page x *et seq.* of this preface) it introduces. The second volume may thus be said only to amplify the newer functions I pointed out in the first volume in 1902 and to illustrate their importance in practice.

The present status of Medicine precludes any apology for the publication of a work such as this. Professor Sollmann, a prominent member of the Council of Pharmacy of the American Medical Association, wrote, only recently (1908): "A generation ago therapeutics was an art, promising to develop into a science. At present it cannot be classed as an art, nor as a science; it can only be classed as a confusion." Indeed, Osler's public declaration¹ that of the action of drugs "we knew little" though we "put them into bodies the action of which we know less," sustained by Llewellys F. Barker's estimate published about the same time,² "that drugs of *unknown* physiological action cannot *conscientiously* be set to act upon bodily tissue in disease in which we are ignorant of *deviations from the normal*," involves the conclusion that our ignorance applies to disease as well as to therapeutics—in a word, to all that which endows us with the right to accept, with any degree of self-respect, the confidence which suffering humanity places in us.

It is not my purpose to take issue with these frank ex-

¹ Osler: N. Y. Sun, Jan. 27, 1901.

² Llewellys F. Barker: Bull. Johns Hopkins Hosp., July-Aug., 1900.

pressions of opinion. In fact, were I to do so, I would conceal similar conclusions reached nearly twenty years ago, when, as editor of the "Annual of the Universal Medical Sciences," it became my lot to collate, with the valued collaboration of many associates, the multitude of data, clinical and experimental, which were accumulating from year to year. Nor do they conflict with the prevailing estimate of the therapeutic worth of Medicine among the best-informed medical men abroad. Skoda's dictum of several years' standing, "that we can diagnose disease, describe it, and get a grasp of it, but we dare not expect by any means to cure it," has drifted along, on the ripples of time, until, hardly two years ago (1907), the president of a prominent British society, Dr. A. H. Brampton,* found it opportune to declare that "if any daring member has introduced a subject bearing on medical treatment, it has been with an apologetic air and humble mien, well knowing that if his remarks had any reference to the utility of drugs in the treatment of disease they would be subjected to good-humored banter, and received by those sitting in the seat of the scornful with amused incredulity." My aim now, as it was when "Internal Secretions" was first projected, is to indicate what to me, at least, appears to be the main cause of the deplorable state of practical Medicine, and if possible to eliminate it.

When, twenty years ago, I was brought face to face with the mass of heterogeneous material we term the "Medical Sciences," and with the yearly crop of contradictory theories upon each disease, mode of treatment, etc., I soon realized that some gigantic flaw could alone account for so great a confusion. In the preface of the 1888 issue, I had stated that the "Annual" was intended "to become a helpmate to the practitioner in his efforts to relieve suffering, and to assist the investigator by correlating facts, thus enabling him the better to compare." Whether much comparison was indulged in by others I cannot say, but the fact remains that, as far as my own position in the matter was concerned, I began then and there to seek for the flaw referred to. I must frankly confess that its identity was not difficult to find, namely: the invalidity of Physiology. Never, when it came to tracing a pathological condition,

* A. H. Brampton: *Lancet*, Jan. 19, 1907.

the effect of a remedy, the nature of a symptom, or any, in fact, of the many phenomena which to us practitioners are of paramount importance in diagnosis or therapeutics, was it possible to trace to its source the chain of events through which a normal function had more or less suddenly become abnormal. Invariably was it found that either the physiologists had failed altogether to discern the nature of that function, or, if an attempt had been made by them to explain it, that it was laden with so many inconsistent and obviously mutually contradictory conclusions that—although perhaps quite scientific in their eyes—it was more misleading than helpful in the explanation of the morbid condition analyzed.

To illustrate these statements, I will submit a few of the more salient deficiencies referred to. The process of respiration, which includes pulmonary respiration and oxygenation of the blood and tissues, at once asserts itself as of capital importance, since it involves the functions of all organs, the vital process, and also every morbid process. In January, 1903, I urged that this function as taught by physiologists failed to satisfy our needs, and suggested new paths for research. Two years later, Professor Chas. R. Barnes, of the botanical department of the University of Chicago,⁴ wrote: "I found it needful to examine the recent literature of respiration in animals, the aspect of the general subject with which I felt myself least familiar. I found to my great surprise, that animal physiologists have concerned themselves very little with the essential problems of respiration." Then, naming our best-known text-books on physiology, he added: "I found no treatment whatever, indeed, no mention whatever, of the real problems of respiration, that is, of what is happening in the tissues, the process of which these external phenomena are the sign." The late Sir Michael Foster⁵ also closed a study on metabolism in the last edition of his text-book with the statement that, after all, it "consists mostly of guesses and gaps." Even the apparently simple process through which the blood acquires its oxygen from the air in the pulmonary alveoli is at present unknown to physiologists, their gasometric experiments being,

⁴ C. R. Barnes: Science, Feb. 17, 1905.

⁵ Sir Michael Foster: cited by W. G. Little: Liverpool Med.-Chir. Jour., Jan., 1905.

as stated by Pembrey,⁶ "very discordant" and inadequate to explain "the absorption of oxygen by the lungs."

If the full meaning of these deficiencies is apprehended, their appalling consequences will appear. The pulmonary air-cells are the main barriers to infection: their surface is the seat of multiplication of the pneumococcus, while their walls afford a nidus for the tubercle bacillus. It is here, therefore, that the initial lesions of the two great destroyers of mankind, pneumonia and tuberculosis, are formed. Now, adequate knowledge of the processes with which oxygen is concerned precisely in this location, would be a boon indeed: it would enable us probably to discern just how Nature defends the body against infection. As to the morbid processes connected with tissue respiration, I pointed out in the first volume,⁷ two years before Beard suggested its use as a remedial agent, that trypsin was the direct destructive agent in another dread disease, cancer. Trypsin is now known to take part in tissue-metabolism. If we had something better than the "guesses and gaps" referred to at our disposal to study this next greatest foe of humanity, I venture to suggest that it would soon be conquered.

Another great function is nutrition. Our first need to interpret intelligently gastro-intestinal infections, is a clear understanding of ferments. A most able physiologist, Benjamin Moore,⁸ wrote recently: "Little is known regarding the chemical nature of enzymes, because all attempts to isolate them in a state of purity have hitherto failed." Another authority, Halliburton,⁹ also writes: "The process through which the digested food-stuffs are absorbed from the alimentary canal is quite as obscure." Thus, Howell¹⁰ writes: "The energy that controls absorption resides . . . in the wall of the intestine, presumably in the epithelial cells, and constitutes a special form of imbibition which is not yet understood." According to Beddard,¹¹ "we know nothing of the path taken by the products of proteid and carbohydrate digestion." Howell¹² also

⁶ Pembrey: Schäfer's "T. B. of Physiol.," vol. I, p. 776, 1898.

⁷ Sajous: *Cf.* vol. I, pp. 609 to 666 incl., 1908.

⁸ Moore: Hill's "Recent Advances in Physiol., etc.," p. 117, 1906.

⁹ Halliburton: "Biochemistry of Muscle and Nerve," p. 30, 1904.

¹⁰ Howell: "T. B. of Physiol.," p. 713, 1905.

¹¹ Beddard: Hill's "Recent Advances in Physiol., etc.," p. 643, 1906.

¹² Howell: *Loc. cit.*, p. 716, 1905.

says: "The form in which proteid is absorbed remains a mystery." Again, if, as text-books on physiology teach, the food-stuffs, duly prepared, were taken up at all by the blood, they should be found in the latter. But, as stated by Mendel,¹³ "Beyond the intestinal wall, in the blood and lymph-stream, the cleavage products seem, for the most part, to be missing." Finally, once in the blood, the fluid proteids should be readily diffusible to penetrate freely to the tissue-cell. Howell¹⁴ states: "The proteids of the blood, which are supposed to be so important for the nutrition of the tissues, are practically indiffusible, so far as we know. It is difficult to explain their passage from the blood through the capillary walls into the lymph."

The problem of nutrition is evidently no more solved by physiologists than those of respiration and tissue metabolism. The consequences to us are quite as deplorable. Asiatic cholera, typhoid, infantile diarrhœa, and kindred disorders are closely related with all intestinal functions, and in absorption lies the key-note to general infection. How can we possibly obtain a clear conception of all these dread diseases with such a foundation as physiology affords us?

The third great question is the manner in which function is incited in an organ. As shown by Claude Bernard, over fifty years ago, this is due to dilation of the arteries of that organ; more blood passing through it, it functionates. Notwithstanding considerable work done upon the problem ever since, the manner in which this function is carried out is quite unknown. Naturally, to admit more blood into an organ, the nutrient arteries must be dilated. Now, in his summary of vasomotor actions, Foster,¹⁵ for instance, says, referring to the presence of dilator nerves in muscles: "There is no adequate evidence that these vasodilator fibers serve as channels for tonic dilating impulses or influences." While Landois,¹⁶ in the last edition of his text-book, holds that "although a center for vasodilator or vessel-relaxing nerves has not yet been demonstrated, the existence of such a center in the medulla may nevertheless be suspected," J. G. Curtis¹⁷ states that "it is not known whether

¹³ Mendel: *Med. News*, May 20, 1905.

¹⁴ Howell: *Loc. cit.*, p. 886.

¹⁵ Foster: "T. B. of Physiol.," sixth American edition, p. 229, 1895.

¹⁶ Landois: "T. B. of Physiol.," tenth edition, p. 771, 1905.

¹⁷ J. G. Curtis: "Amer. T. B. of Physiol.," vol. 1, p. 199, 1900.

a vasodilator center is present in the bulb." The actual state of the question is aptly summarized by H. C. Chapman,¹⁸ when he says: "Though numerous explanations have been offered of the manner in which the vasodilator nerves act, it must be admitted that none of them are satisfactory, and that it is not yet understood how this stimulation causes dilatation of the blood-vessels."

Now, the bearing of this physiological process upon pathogenesis and therapeutics may be said to be limited only by the total number of diseases to which the human frame is exposed, since all disorders are functional or organic, and all organic diseases impair function at a given time. A possible exception suggests itself, namely, the nervous system. But here, again, the *deus ex machina* of the function as a whole, the nerve-impulse, has remained hidden. As Landois¹⁹ says, "the nature of the physiological nerve-stimulus in the normal body is not known." This accounts for the prevailing discouragement among the devotees of a great specialty, neurology, as expressed in the recent statement of a very diligent worker in that line, Joseph Collins,²⁰ "that we know very little more concerning the etiology, pathogenesis, and the clinical display of the majority of nervous diseases, organic and functional, than we did twenty years ago."

These are but a few of the evident shortcomings of Physiology; others will be referred to in the body of the work. I wish to state, however, that their enumeration is not inspired by a spirit of criticism; they are mentioned because each deficiency is subjected to a searching inquiry in the second volume with a view to its elimination: Indeed, any one who has examined physiological lore as closely as I have, cannot but admire the enormous and patient labor that physiologists have devoted to the solution of the multitude of problems which the functions of the human organism involve, including the many unsolved ones to which I refer. But I must now, after writing the second volume, emphasize a feature which I merely suggested in the first volume, viz., that their failure to explain the many functions referred to is due to the fact that they have

¹⁸ H. C. Chapman: "Human Physiology," second edition, p. 692, 1899.

¹⁹ Landois: *Loc. cit.*, p. 631.

²⁰ Joseph Collins: *Monthly Cyclo. of Pract. Med.*, Feb., 1905.

overlooked the cardinal functions of the organs to which I have given special attention: the adrenals, the thyroid, the pituitary body and the leucocytes.

As the text will show, various branches of biology have been studied, but many of the facts which have served to elucidate function were obtained from clinical medicine. A great physiologist, Professor Pawlow, of St. Petersburg, wrote a few years ago,²¹ after stating that physicians had pointed out the existence of gastric secretory nerves—a question which, I may add, has been greatly elucidated, thanks to his own labors: “Physiologists, on the other hand, had fruitlessly endeavored for decades to arrive at definite results upon this question. This is a striking, but by no means isolated, instance where the physician gives a more certain verdict concerning physiological processes than the physiologist himself; nor is it indeed strange. The world of pathological phenomena is nothing but an endless series of the most different and unusual combinations of physiological occurrences which never make their appearance in the normal course of life. It is a series of physiological experiments which Nature and life institute, often with such an interlinking of events as could never enter into the mind of the present-day physiologist, and which could scarcely be called into existence by means of the technical resources at our command. Clinical observation will consequently always remain a rich mine of physiological facts.” There are precedents, therefore, upon which a legitimate belief may be based that the conclusions I have reached are sound. They afford, moreover, a clear explanation of the inability of physiologists to discern the functions my researches have led me to discover: they are partly hidden in a field that physiologists could not legitimately be expected to scrutinize, owing to its vastness. In this connection, it is mainly, therefore, as a contribution of pathological biology to normal biology, of which physiology is a subdivision, that the two volumes of “Internal Secretions” are offered.

Among the more important features which the views I advance therein appear to me to point out for the first time

²¹ Pawlow: “The Work of the Digestive Glands,” Thompson’s transl., p. 46, 1902.

(as far as the literature and the experimental and clinical facts within my reach have enabled me to judge) are the following:—

As bearing directly upon Biology:—

1. The main function of the adrenals, viz., to supply an internal secretion which absorbs the oxygen of the air to carry it to the tissues; and, as a result of this fact:—

2. Pulmonary respiration, and

3. Tissue respiration;

4. The identity of the albuminous moiety of the hæmoglobin molecule, viz., the oxygenized adrenal secretion;

5. The identity of the oxidase of the blood, *i.e.*, the oxygenized adrenal secretion referred to (after the thirteenth chapter) as “adrenoxidase”;

6. The identity of the red corpuscles as storage-cells for adrenoxidase and as purveyors of this body to the tissues;

7. The general composition of ferments;

8. That the adrenal principle is the one ferment which endows all other body-ferments with their properties as such;

9. The identity of “secretin” as adrenoxidase;

10. The identity of “enterokinase” as adrenoxidase plus nucleoproteid;

11. That the granulations of the leucocytes serve to build our tissues and to nourish them;

12. That the substances out of which the leucocytes form their granulations (anabolism) are the proteids and carbohydrates ingested by them in the intestinal canal, its epithelium and villi, and in the blood;

And, in virtue of these facts:—

13. The process of absorption, and

14. The process of general nutrition;

15. That it is the function of leucocytes to convert the constituents of the ingested proteids into living proteids;

16. That the granulations they supply to the tissue-cells are living substance;

17. That the principle which endows the constituents of proteids with life in the leucocytes is the adrenal active principle;

18. That the adrenal principle is the dynamic element in the vital process;

19. That the granulations of leucocytes once in the tissue-cells live temporarily therein and are, when worn, broken down by ferments (catabolism), and voided by the cellular vacuoles into the pericellular lymph-spaces;

And, in virtue of the foregoing conclusions:—

20. The process of metabolism;

21. That all the ferments and carbohydrates found in the tissues and other immobile cells are brought to them by leucocytes and are derived from the alimentary system, especially the pancreas (trypsin) and liver (glycogen);

22. That a portion of the pancreatic ferments forms an internal secretion which passes to the splenic vein and thence into the portal system;

23. That the splenic internal secretion (probably nucleoproteid) also passes out into the splenic vein and thence into the portal system;

24. That on reaching the portal system from the alimentary canal, the leucocytes absorb the pancreatic ferments and splenic internal secretion (probably nucleoproteid) which they supply to the tissue-cells and with which they carry on their intrinsic functions;

25. That the nervous system, in keeping with other tissues, is composed of cells likewise developed and nourished by leucocyte-granulations, and traversed by the oxygen-laden adrenoxidase;

26. That the ground substance and Nissl granules of nerve-cell-bodies and the myelin of their axis-cylinders or nerves are to the nerve-cell what the cytoplasm is to other tissue-cells;

27. That the neuro-fibrils, including those of the axis-cylinders, are nerve-capillaries through which the nerve-cells are supplied with oxygen-laden adrenoxidase;

28. That these neuro-fibrils receive their adrenoxidase-laden plasma from the general circulation through the intermediary of the neuroglia fibers (also capillaries) and the neuroglia-cells which regulate the volume of plasma admitted into the neuroglia fibers;

And, in virtue of the last four conclusions:—

29. The circulation of the nervous system;

30. That the myelin of nerves is not a mere insulating material or sheath, but a compound rich in phosphorus which, when in contact with the oxygen-laden adrenoxidase circulating through them, generates nerve-energy;

31. That the ground-substance, the Nissl granules and the myelin in the cell-bodies of neurons and their dendrites, are also phosphorus-laden compounds which, when in contact with the adrenoxidase circulating through them, generate nerve-energy;

And, in virtue of the last two conclusions:—

32. The source and nature of the nerve-impulse;

33. That the pituitary body is the general and governing center of the spinal system, which includes the gray substance of the base of the brain, pons, bulb and spinal cord, and the nerves derived from any of these structures, cranial or spinal, though subsidiary centers are also present in the bulb and spinal cord;

34. That the pituitary body is the governing center of all vegetative functions, i.e., the somatic brain;

And, in virtue of these two conclusions:—

35. The identity of the pituitary body as the most important of all organs concerned with the vital functions of invertebrates and vertebrates, including man;

36. That the brain (as differentiated from the somatic brain) is the organ of mental processes and not the governing organ of motor functions; though capable, through the voluntary impulses it transmits to the spinal system, of having its mandates carried out;

And, in virtue of these two conclusions:—

37. The identity of the brain (as differentiated from the somatic brain) as solely the organ of Mind.

38. That neither the anterior nor the posterior pituitary body is a secreting gland;

39. That the anterior pituitary body is a lymphoid organ which, through the intermediary of a center located in the posterior pituitary body and a nerve-path in the spinal system, the upper dorsal sympathetic ganglia and the splanchnic nerves, governs the functional activity of the adrenals;

And, in virtue of this conclusion:—

40. That the anterior pituitary body governs, through the posterior pituitary body, all the oxidation processes of the body;

41. That the center in the posterior pituitary body through which the anterior pituitary body governs the adrenals also controls the functional activity of the thyroid gland, and thus constitutes the "adrenothyroid" center;

42. That the pituitary body, the adrenals and the thyroid gland (including the parathyroids) are thus functionally united, forming the "adrenal system;"

43. That the posterior pituitary body is the seat of the highly specialized centers which govern all the vegetative or somatic functions of the body, and of each organ individually;

44. That the posterior pituitary body receives all the sensory impressions belonging to the field of common sensibility: pain, touch, muscular sense, etc., initiated in any organ, including the mucous membranes, skin and brain;

45. That owing to this fact, the posterior pituitary body is the *sensorium commune* upon which all emotions, shocks—psychical or traumatic—concussions, etc., react, the resulting impairment of its functions being the cause of the morbid phenomena observed under such conditions;

46. That the sympathetic system is also governed by a center, and

47. That the sympathetic center is likewise located in the posterior pituitary body and constitutes one of the most sensitive of its centers;

48. That it is the function of the sympathetic center and of the sympathetic system to govern the caliber of all arterioles, and to regulate, through the spiral muscular coat of these vessels, the volume of blood admitted into the capillaries of any organ, including those of the brain and nervous system;

49. That the vasomotor center governs the caliber of the larger vessels only, *i.e.*, of all vessels that are larger than the arterioles;

50. That active vasodilation exercised through vasodilator nerves is limited to the arterioles;

51. That dilation of an arteriole is due to constriction by the terminal fibers of a cranial nerve (the vagus, for example) of the vasa vasorum which supply its walls with adrenoxidase-laden plasma, thus causing ischæmia and relaxation of its muscular coat;

52. That while this process, "stricto-dilation," serves to admit an excess of blood into an organ when the functional activity of the latter is to be increased, the sympathetic fibers, when the organ's functions are to cease, restore the arterioles to their normal caliber;

And, in virtue of the facts embodied in the last seven conclusions:—

53. The mechanisms of vasodilation and function.

As bearing directly upon Immunity:—

54. That the sensory organ in the partition between the two lobes of the pituitary body is morphologically the homologue of the "test-organ" or "osphradium" of mollusks and other Invertebrates, which has for its purpose to protect the animal against noxious materials that may be present in the water admitted into its organism;

55. That all Vertebrates, including man, are protected, as are Invertebrates, against noxious materials that may be present in the blood (a chemical homologue of sea-water), their test-organ, a sensory structure, being sensitive to certain poisons as the olfactory area, which it resembles histologically, is to odors;

56. That the test-organ of Vertebrates, including man, reacts under the influence of any poison brought to it by the blood or its leucocytes (phagocytes) capable of exciting it, by increasing, through the adreno-thyroid center, which it governs, the functional activity of the adrenals and of the thyroid and parathyroids;

57. That by increasing the functions of the adrenals it enhances the bacteriolytic and antitoxic powers of the blood and its phagocytes;

58. That by increasing the functional activity of the thyroid and parathyroids it increases, through their secretions, the sensitiveness of all cells, including bacteria, and their vulnerability to phagocytes, inasmuch as

59. The secretions of the thyroid and parathyroids jointly form the opsonin and agglutinin of the blood;

And, in virtue of the last six conclusions:—

60. That the adrenal system, composed of the pituitary body, the adrenals and the thyroid apparatus, constitutes the immunizing mechanism of the body; and, furthermore,

61. That inasmuch as the adrenal system has for its purpose to protect the body against disease, it is by enhancing the functional activity of the adrenal system that we can overcome disease;

62. That the adrenal system causes the appearance, in the blood and phagocytes, of an excess of "auto-antitoxin," a (qualitative) chemical homologue of diphtheria antitoxin and other antitoxins;

63. That this "auto-antitoxin" (as well as all other antitoxins) is composed of the internal secretions of the adrenals (adrenoxidase: Ehrlich's amboceptor), of the pancreas (trypsin: Ehrlich's complement), of the spleen and leucocytes (nucleo-proteid), and of the thyroid and parathyroids (thyroidase: Wright's opsonins);

64. That it is to the excess of auto-antitoxin that the increased bacteriolytic and antitoxic properties of the blood and phagocytes (the *true vis medicatrix naturæ*) are due.

As bearing directly upon Pharmacodynamics:—

65. That rational Therapeutics, in so far as the cure of pathogenic processes based on toxæmias is concerned, should include measures which promote the formation of auto-antitoxin in the blood and phagocytes;

66. That we have drugs, of which thyroid extract, mercury, and iodine are types, which provoke energetically the formation of auto-antitoxin;

67. That the production of an excess of auto-antitoxin in the blood, under the influence of bacterial toxins or endotoxins, or of any poison capable of exciting the test-organ (and through it the adrenal system) sufficiently, is the phenomenon known as "fever," and that the "thermogenic" or "heat" center is thus located in the pituitary body;

And, in virtue of this conclusion:—

68. The nature of fever and its mode of production;

69. That we can by means of agents which stimulate concomitantly the test-organ and the vasomotor and sympathetic centers or any two of these centers, enhance metabolism and nutrition and the production of auto-antitoxin, as exemplified by belladonna, strychnine, coca, quinia and other drugs;

70. That we can supply the body with the constituents which its blood and tissues lack and that these agents are adjusted to the needs of each organ by the leucocytes, as exemplified by iron and phosphorus;

71. That all drugs are taken up by leucocytes in the intestinal canal and blood and transported by them to all parts of the body;

72. That the sympathetic center in the posterior pituitary body is the sleep center;

73. That the sympathetic center provokes sleep by lowering the functional activity of the anterior pituitary body and of the adrenal system, and causes thereby a general relaxation of all arteries, accumulation of blood in the splanchnic area, and ischæmia of the cerebro-spinal system;

74. That drugs of which opium is the type, produce sleep by stimulating the sympathetic center;

75. That drugs of the type of chloral, the bromides, etc., produce sleep by depressing the vasomotor center and causing accumulation of blood in the splanchnic area and ischæmia of the cerebro-spinal system;

And, in virtue of the four last conclusions:—

76. The manner in which sleep is provoked;

77. That anæsthetics of which chloroform and ether are types, produce sleep and anæsthesia by exciting powerfully the vasomotor center, causing thereby general vasoconstriction followed by hyperæmia of all capillaries, including those of the cerebro-spinal system, and venosity of their arterial blood;

78. That anæsthetics of which nitrous oxide is a type, produce sleep and anæsthesia by replacing the oxygen of the air and producing venosity of the blood in the capillaries of the cerebro-spinal system and other organs;

79. That pain is due to hyperæmia of the sensory-nerve terminals, of the *nervi nervorum*, etc., and that any agent which indirectly or directly causes diminution of this hyperæmia counteracts pain;

And, in virtue of this conclusion:—

80. The nature and mode of production of pain;

81. That analgesics of the type of opium counteract pain by stimulating the sympathetic center, and by thus causing the dilated arterioles which supply the painful area to resume their normal caliber;

82. That analgesics of the type of antipyrin, acetanilid, etc., counteract pain in the same way, but, being more violent in their action, are apt to cause hyperconstriction of the arterioles and cyanosis;

83. That drugs of the type of amyl nitrite, nitroglycerin, etc., produce dilation of the arterioles by inhibiting the functional activity of the sympathetic center;

84. That drugs of the type of *veratrum viride*, the bromides, etc., lower the vascular pressure by inhibiting the functional activity of the vasomotor center;

85. That alcohol is a fictitious stimulant and in reality a depressant, owing to the fact that it deoxidizes the plasmatic adrenoxidase;

86. That the mineral salts fulfill so important a rôle in the preservation of the osmotic properties of the body fluids and their alkalinity, that their replacement in all diseases in which they are actively reduced is an essential feature of the curative process;

87. That purgatives produce their beneficial effects by causing either reflexly or by centric action, according to the purgative used, an increase of bacteriolytic and antitoxic auto-antitoxin in the intestinal canal;

88. That all emetics produce their effects by provoking irritation of the gastric mucosa: the local emetics (mustard, zinc sulphate, etc.) by irritating it directly; the general emetics (apomorphine, tartar emetic, etc.) by depressing markedly the vasomotor and sympathetic centers and thus causing dilation of the arterioles and hyperæmia of the gastric glandular elements;

89. That diaphoretics act similarly, the sweat glands (as well as all other glands) being rendered hyperæmic and overactive.

Bearing directly upon Pathogenesis and Therapeutics:—

90. That the vulnerability of the organism to infection is inversely proportional to the efficiency of the adrenal system, the relative amount of auto-antitoxin in the pulmonary and intestinal secretions, and the bacteriolytic activity of the phagocytes;

91. That the diseases which are most fatal to mankind: cancer, tuberculosis, pneumonia, Asiatic cholera, bubonic plague, etc., are due to agencies, endogenous or exogenous, which interfere with, or paralyze, the functions of the test-organ and through it the adrenal system;

92. That all these diseases can be treated successfully, when seen not too late, by means of remedies which excite with adequate activity

the test-organ, and provoke through it an accumulation of auto-antitoxin and thyroïdase (opsonin) in the blood;

93. That the convulsive diseases: tetany, tetanus, epilepsy, puerperal eclampsia and rabies, are all due to the accumulation of toxic waste-products in the blood;

94. That all these convulsive diseases can be arrested by measures which prevent the accumulation of toxic wastes in the blood and which increase the proportion of auto-antitoxin in the latter,—provided organic lesions in the cortex (gliosis) have not been given time to develop;

95. That all the diseases grouped under "gouty diathesis:" gout, migraine, neuralgia, sciatica, etc., are due to hypoactivity of the test-organs and the adrenal system;

And, in virtue of these six conclusions:—

96. That the most fatal and distressing diseases of mankind have not been mastered because the cardinal rôle of the adrenal system in their pathogenesis, prevention and cure, has been overlooked.

As previously stated, this list includes only the more important functions that my researches—including personal investigations in the laboratory, clinical observations, and analysis of the vast fund of knowledge available in literature—have brought to light. Were all enumerated, including those introduced in the departments of "Pharmacodynamics" and "Pathogenesis and Therapeutics" (where they are designated by asterisks in each drug and disease studied), they would aggregate several hundred. This fact is only referred to in order to illustrate the far-reaching importance of the functions of the internal secretions in all processes, normal, morbid, or protective, and the large number of gaps they fill.

The final conclusions to which I have been led—those submitted in the second volume—are not offered as mere theories, but as solutions carefully worked out from the abundant material at my disposal. My labors as editor of the "Annual of the Universal Medical Sciences" and the "Cyclopædia of Practical Medicine" having shown that it was to the habit of theorizing with a few facts as foundation into which investigators, and particularly laboratory workers, have fallen, that the confusion which characterizes the Medicine of our day was due, the following working plan was adopted: The literature of each subject, my own experimental and clinical observations, etc., were collected, subdivided and filed. When a given subject was taken up, each paper available was analyzed and the sound experimental or clinical facts or observations were noted and arranged in series. In physiological questions, the teachings of physiological botany, zoölogy and cytology were added. All

these data (amounting to several hundreds in some instances) were treated as factors in the search of a solution—the solution submitted at the end of each section, in italics in the first seventeen chapters, and thereafter in large type. The final solution reached in each instance was submitted to a rigid test, however, viz., *absolute concordance with all other solutions in the work*—a process which brought to light any defect, not only in the solution itself, but likewise in all conclusions previously adduced. The chances of error were thus reduced to a minimum, while a solid framework was elaborated for future discoveries by other investigators.

These details are given not only with the object of aiding others who might wish to work on parallel lines, but to illustrate another salient feature brought to light by my editorial work upon the “Annual” and the “Cyclopædia,” namely, that *the present unsatisfactory condition of Medicine is due to the fact that investigators do not avail themselves of the enormous array of solid data available to ascertain the truth*. Blinded by the fallacious idea that the worth of a contribution to our knowledge should be gauged solely by the new experiments and clinical observations it adds to those already available, they lose sight of the fact that such experiments and observations are but bricks and mortar out of which a coherent and truly useful Medicine—one indeed worthy of ranking as a science—can be built.

The conception of Medicine presented in the second volume—and foreshadowed in the first—is submitted only as an *effort* in this direction. It aims to replace the empirical and hazardous use of remedies which has undermined increasingly the confidence of our best observers in them, by a system of therapeutics based on solidly established facts which makes it possible to trace every phase of their action to its source. The centers influenced may thus be used by the physician as so many levers through which he can regulate the defensive agencies of the organism and the mechanisms which distribute them, precisely as a general can govern the defensive movements of an army in the field. As the disease-causing substances, toxins, endotoxins, toxic wastes, etc., are also shown to produce their effects through a morbid action upon the centers influenced by our remedies, they may thus be met directly where they strike and antagonized before they can destroy life.

The work introduces no elixir of life, no universal panacea, nor even a new serum, the weapons recommended are available to all, viz., the identical remedies which for years have been in daily use—the forty or fifty that have stood the test of time. It shows, I believe, that it is not because we have been lacking agents capable of successfully coping with disease that confidence in remedies has been steadily decreasing, but because they were used blindly and often, therefore, injudiciously. There is now not the least ground for doubt as to the efficiency of our therapeutic resources. I shall be amply repaid if I have succeeded in proving this fact, and if “Internal Secretions” to any degree instills into its readers the unbounded confidence in the power of our remedies to antagonize and even master disease that a broad survey of the scientific facts at our disposal and considerable practical experience have instilled into me.

The plan of the second volume, as stated in the preface, included only “Applied Therapeutics,” *i.e.*, the physiological action of drugs in morbid processes, but thanks to the liberality of my publishers, the F. A. Davis Company, I was able to add a department in which the pathogenesis and treatment of the most fatal and distressing diseases with which we have to contend are treated in full. Hence the comparatively large size of the second volume.

It is with great pleasure that I acknowledge the encouragement and moral support I have received during the rather arduous task the preparation of this work imposed upon me, from my friends, Mr. F. A. Davis, president of the F. A. Davis Company, my publishers, and Dr. J. Madison Taylor, my associate in the editorial management of the “Monthly Cyclopædia of Practical Medicine.” Several of the microphotographs presented in this volume were prepared by my son, Dr. Louis T. de M. Sajous, from slides. Some of these I owe to the kindness of Professors George A. Piersol and D. J. McCarthy, of the Medical Department of the University of Pennsylvania, to whom I wish to express my thanks.

C. E. DE M. SAJOUS.

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CHAPTER I.

THE ADRENALS IN CLINICAL PATHOLOGY AND THERAPEUTICS.

SIMILARITY OF THE EFFECTS OF REMOVAL OF THE ADRENALS IN ALL VERTEBRATES, INCLUDING MAN.

BROWN-SÉQUARD,¹ in 1856, demonstrated the physiological importance of the suprarenal capsules by showing that removal of these organs from animals was soon followed by death. To offset the conclusions of Phillipeaux and Gratiolet, who ascribed death to secondary involvement of the central nervous system, he extended his researches,² and showed, first, that transfusion of blood taken from a normal animal into a dying, decapsulated animal brought the latter to life, and, second, that the blood of a dying, decapsulated animal was poisonous to another decapsulated animal, the life of the latter being shortened by eight hours as compared to the average longevity of other animals similarly mutilated.

A certain degree of antagonism to Brown-Séquard's conclusions long prevailed among a limited number of investigators, who ascribed death in animals from which both adrenals had been extirpated to surgical shock—a view apparently sustained by the close relationship that exists between these organs and the sympathetic system. That such may be the case under some circumstances: *i.e.*, the use of an animal debilitated by starvation or rough handling, lack of dexterity in the extirpation of the organs, is to be surmised; but, when all features that tend to compromise the issue are absent, there is not the least ground for the view that shock is the cause of death in decapsulated animals. As shown by Langlois,³ no marked symptoms usually occur during the first twenty-four hours. The fatal

¹ Brown-Séquard: *Comptes-Rendus de l'Académie des Sciences*, vol. xviii, 1856.

² Brown-Séquard: *Journal de Physiologie*, vol. i, 1858.

³ Langlois: *Archives de Physiologie norm. et path.*, vol., 1897.

issue is not immediate; and in frogs, rabbits, guinea-pigs, and dogs the post-operative life varies from an average of forty hours in mild weather to twelve or thirteen days in the hibernating frog in winter. In a series of fifty-nine rats from which Boinet⁴ removed both adrenals, four lived several months. Some evidence of shock should have appeared in at least a small proportion of the operated animals. Not only was this not the case, but the fact that in four of them the prolongation of life was found to have been due to accessory or compensatory organs demonstrates the weakness of the shock hypothesis as the main cause of death in decapsulated animals. Furthermore, the average symptomatology of post-operative life in various species—inco-ordination, muscular weakness or excitement, and tremors; then paralysis of the hind-quarters, with gradual involvement of the trunk and upper extremities, contraction of the pupil, gradual and steady slowing of the cardiovascular rhythm, convulsions, hæmaturia, epistaxis, etc.—in no way resembles that of shock.

Finally, complete removal of but one organ seems to affect animals so slightly that they appear to suffer no inconvenience; they continue to live month after month, "quite well and active"; *i.e.*, until the experimenter removes the second adrenal, when death occurs within thirty-six hours. This fact, added to many others elucidated by the labors of Abelous and Langlois,⁵ Oliver and Schäfer,⁶ Cybulski,⁷ Szymonowicz,⁸ Gourfein,⁹ Langlois,¹⁰ Swale Vincent,¹¹ Boinet,¹² Parhon and Golstein,¹³ and others, shows that there is no legitimate ground—after eliminating all factors that obviously tend to disguise the source of physiological phenomena and pervert their meaning—to doubt that, as Brown-Séquard was first to show, extirpation of both

⁴ Boinet: *Marseille Médical*, Sept. 1, 1899.

⁵ Abelous and Langlois: *Archives de Physiologie norm. et path.*, vol. xiii, p. 267.

⁶ Oliver and Schäfer: *Journal of Physiology*, vol. xviii, 1895.

⁷ Cybulski: *Gazeta Lekarska*, March 23, 1895.

⁸ Szymonowicz: *Archiv f. d. Gesam. Phys.*, vol. lxiv, 1896.

⁹ Gourfein: *Revue Médicale de la Suisse Romande*, March, 1896.

¹⁰ Langlois: *Loc. cit.*, 1898.

¹¹ Swale Vincent: *Journal of Physiology*, Sept. 11, 1897; Feb. 17, 1898; Apr. 25, 1898.

¹² Boinet: *Loc. cit.*

¹³ Parhon and Golstein: "Les Sécrétions Internes," p. 736, 1909.

suprarenals is followed by death, and that these organs fulfill in the organism a rôle of great physiological importance.

Are the suprarenal glands functionally as important in man as they are in the lower vertebrates? The clinical field alone offers the necessary elements for the study of this question; but it is strewn with obstacles. The various kinds of neoplasms which develop in these organs, with the possible exception of sarcoma, are of slow growth; the sufferer passes through various phases that are more or less influenced by concomitant conditions and by the pressure which the tumor exerts upon important neighboring structures. In carcinoma there may also be involvement of other viscera by continuity of tissue or metastasis. We therefore obtain, in relation to the symptom-complex of pure suprarenal origin, a transformed picture, one that precludes all certainty as to the relations between cause and effect. Addison's disease affords, if anything, less opportunity for solid analysis; it may be associated with suprarenal lesions and it may not; in some cases but one organ is involved; in others, both; if it is due to suprarenal tuberculosis, this process may be secondary or primary, thus furnishing a series of misleading symptoms due to the extrinsic lesions; finally, we may at a *post-mortem* find the organs completely destroyed and obtain an *ante-mortem* history in which the Addisonian syndrome is conspicuously absent.

What is required for a fruitful analysis of this question is a condition in which the adrenals are alone the seat of a mortal lesion: a lesion capable of suddenly annihilating the functions of both organs precisely as does their experimental removal in animals. A single disorder of the adrenals, among the few that have been so far described, fulfills these requirements in some of its manifestations, namely: hæmorrhage. The literature of this subject is, however, exceedingly meager: hardly two hundred cases having been reported. We are therefore fortunate in having at our disposal an able and exhaustive review of eighty of these cases, including several of his own, by François Arnaud,¹⁴ of Marseilles, which affords the necessary data. While some of the cases are very briefly reviewed, the

¹⁴ François Arnaud: Archives Générales de Médecine, p. 64, July, 1900.

- details furnished are at least sufficient to enable us to obtain what appears to be strong evidence to the effect that, precisely as it does in the lower animals, destruction of the adrenals in man causes death within a very brief period.

Indeed, out of the eighty cases collected by this investigator, death occurred within a period ranging from a few hours to three days in fifteen. In all of these the pathological data given show that both glands had been the seat of the hæmorrhagic process: of "suprarenal apoplexy," as he terms it. Ten of these cases, however, lose some of their value as testimony because no allusion is made to the condition of the other organs. In the other five, including details that we have obtained from the original reports, it is specifically stated that *lesions were found nowhere else in the organism*. To the following tabulated list of these cases I have added two instances of the same kind (Andrewes and Colman):—

CASE 1 (Arnaud¹⁵).—Male, 36 years. Death occurred 48 hours after entrance. Both glands were apoplectic and greatly enlarged. One weighed 28½ grammes; the other 48 grammes. Both when cut resembled flesh, and were studded with hæmorrhagic foci and spots of hæmatomatous organization indicating a progressive lesion of long standing. A small amount of medullary substance was still present in the right capsule, but otherwise the organs were structurally destroyed.

CASE 2 (Arnaud¹⁶).—Female, 17 years. Death occurred suddenly on the eleventh day after the receipt of a burn on the arm; the symptoms suggested acute poisoning, but the autopsy revealed hæmorrhage into the right capsule and congestion of the left.

CASE 3 (Andrewes¹⁷).—Female, 15 months. Death 36 hours after onset of symptoms. Both capsules showed interstitial hæmorrhage. All cultures were sterile, or, if any organisms were present, not one grew on ordinary media or stained with ordinary reagents.

CASE 4 (Mattei¹⁸).—Male, aged 60 years. Death in 24

¹⁵ Arnaud: Archives Générales de Médecine, pp. 16 and 53, July, 1900.

¹⁶ Arnaud: Archives Générales de Médecine, p. 50, July, 1900.

¹⁷ Andrewes: Lancet, May 7, 1898.

¹⁸ Mattei: Lo Sperimentale, 1863. Case I in Trans. Gaz. hebdom., Paris, No. 35, p. 380.

hours after onset of acute symptoms. Both capsules were enlarged, and transformed into bags containing clots surrounded by the cortex, which had thus been forcibly detached from the medullary substance.

CASE 5 (Garrod and Drysdale¹⁹).—Case, aged 4 months. Brought into hospital dead. Both glands dark-purplish red, though not enlarged; meshes of stroma filled with red corpuscles.

CASE 6 (Droubaix²⁰).—Case, 11 hours old at onset of symptoms. Death in 3 days. Hæmorrhage into both organs, with infiltration into the pericapsular cellular tissue.

CASE 7 (Colman²¹).—Case, 11 months. Death in about 25 hours. Both capsules showed diffuse interstitial hæmorrhage, and cultures proved sterile.

Strongly suggestive, also, is the fact that, of the seventeen cases of comparatively sudden death, fifteen showed suprarenal apoplexy in both organs, while two only showed involvement of but one organ. These two instances might invalidate the evidence adduced, could the sudden death in them not be shown to have been due to other causes. But such is the case: In the one (Parrot's²² case No. 11) the hæmorrhagic adrenal had ruptured, and the patient died of hæmorrhage into the peritoneal cavity; in the other (Droubaix's²³ case No. 9) death had resulted from uræmia, due to granular and cystic degeneration of the kidneys.

Additional evidence is afforded by the fact that complete destruction of but one adrenal proves harmless to man, as it does in animals. The results of operative procedures instituted for the removal of suprarenal neoplasms prove this to be the case. A lipomatous capsule, for instance, was removed, along with a wedge-shaped piece of underlying kidney, by Mayo Robson²⁴ in 1897. "The wound healed by first intention and the patient rapidly regained her lost flesh and strength. She remains well, and had had no return of the trouble." This

¹⁹ Garrod and Drysdale: *Lancet*, May 7, 1898.

²⁰ Droubaix: *Thèse de Paris*, Case I, p. 26.

²¹ Colman: *Lancet*, May 7, 1898.

²² Parrot: *Archives Générales de Médecine*, vol. xcix, 1872.

²³ Droubaix: *Thèse de Paris*, 1887.

²⁴ Mayo Robson: *British Medical Journal*, Oct. 21, 1899.

report was published almost two years after the operation. A fibromyxosarcomatous adrenal was removed, along with the entire right kidney, by Howard A. Kelly.²⁵ The case proceeded to full recovery notwithstanding the malignant nature of the growth. A tuberculous adrenal and the right kidney were also removed by A. F. Jonas.²⁶ The patient was discharged six weeks later in full convalescence. Finally, Knowsley Thornton²⁷ removed a sarcomatous gland from a woman aged 56 years. The patient was seen six years later and found in good health.

This does not mean, however, that a diseased gland may not cause death. In this particular the adrenals are similar to any other organ. A rapidly growing sarcoma or a carcinoma may start in one of the organs, develop by metastasis elsewhere, and cause death. Tuberculosis frequently finds a *nidus* in either adrenal or both simultaneously; this process, along with the asthenia engendered by the suprarenal disease, may rapidly end in death. Again, when we consider the frequency with which fatty degeneration is found in these organs when microscopically examined,—thirty-six times out of one hundred autopsies taken *at random*, according to Arnaud,²⁸—it would certainly be unwise to establish such limits.

But this also suggests that death may thus follow any destructive process (hæmorrhage included) of a single adrenal, if the functions of its mate are sufficiently inhibited through a local lesion or by a morbid condition involving its peripheral vascular or nervous supply. Indeed, the anatomical relations of these glands indicate that their functions are primarily dependent upon the integrity of these trophic structures. The multitude of nerves distributed to them include medullated fibers from the solar plexus, the sympathetic's densest network. Dogiel²⁹ states that the internal zone of the cortex is surrounded by a more or less dense fibrillary plexus, and that the medullary substance is provided with an extraordinary sup-

²⁵ Howard A. Kelly: Quoted by Ramsay, Johns Hopkins Hosp. Bull., Jan., Feb., Mar., 1899.

²⁶ A. F. Jonas: Annals of Surgery, April, 1898.

²⁷ Knowsley Thornton: Harvelian Lectures.

²⁸ Arnaud: *Loc. cit.*, p. 6.

²⁹ Dogiel: Archiv f. Anatomie u. Physiologie, p. 90, 1894.

ply of nerves. He likewise found the aggregate of these nerve-fibrils to be greater than that of the glandular elements proper. It seems evident, therefore, that any organic lesion affecting or involving the peripheral nerve-structures of one organ—tuberculosis, cancer, etc.—can so compromise its functions as to make it practically useless if suddenly called upon by hemorrhage into its mate to assume the physiological rôle of both.

All these facts appear to demonstrate that in man, as well as in the lower vertebrates, life continues as long as one of the adrenals is normal, or, at least, as long as any morbid condition affecting this organ intrinsically or extrinsically is not sufficiently advanced to materially compromise its physiological functions. But, as is also the case in lower vertebrates, man soon dies if the physiological functions of both organs are arrested through any intrinsic or extrinsic disorder, unless some compensating organ or condition be vicariously active. It seems evident, therefore, that *the physiological functions of the adrenals are sufficiently similar in all vertebrates to warrant the use of experimental data obtained with lower animals in the study of these organs in man.*

FUNCTIONS OF THE ADRENALS THAT ARE SUPPRESSED WHEN THESE ORGANS ARE REMOVED.

Cybulski and Szymonowicz³⁰ found that blood drawn from the suprarenal vein gave rise, when injected into the bloodstream of normal animals, to manifestations similar to those observed after the injection of suprarenal extract. As a controlling experiment, these observers also injected blood taken from veins other than the suprarenal, but with negative results. Langlois³¹ corroborated these observations as regards the effects of blood obtained from the suprarenal vein. Dreyer³² reached the same results, though not in all animals: a feature of his experiments easily accounted for by the known fact, applicable to all glands, that the amount of substance produced by the organs may vary at different times and under different

³⁰ Cybulski and Szymonowicz: *Loc. cit.*

³¹ Langlois: *Archives de Phys. norm. et path.*, p. 152, 1897.

³² Dreyer: *Am. Jour. of Physiol.*, vol. ii, p. 203, 1899.

circumstances. This obviously suggests that the morbid phenomena witnessed after extirpation of the adrenals are due to the absence of a substance produced by these organs and secreted into the adrenal veins. In his recent work, Swale Vincent^{32a} states that considerable evidence attests to the fact that "it passes by way of the adrenal veins into the general circulation."

Not only do the adrenals produce the blood-pressure-raising substance the lack of which accounts for the symptoms that follow bilateral removal, but the secretion of these organs alone possesses the property of arresting these symptoms. Cybulski³³ found experimentally that the increase of blood-pressure and other cardio-vascular manifestations, etc., could not be obtained from similar preparations from the brain, spinal ganglia, lymph-glands, liver, spleen, kidney, testicle, or thyroid. Mankowsky³⁴ corroborated these observations and noted that the blood-pressure-raising power was peculiar to the suprarenal extract, his experiments having also shown that this action could not be obtained from the fresh thyroid gland, pancreas, lymphatic glands, parotid, kidneys, liver, spleen, cerebrum, heart, or skeletal muscles.

An extract obtained from human adrenals possesses similar properties to the preparations in general use. This important fact was ascertained by Guinard and Martin, of Lyons,³⁵ who conducted a series of experiments with the adrenals of a healthy executed criminal. Expressed juice of these glands "produced physiological phenomena similar to those noted with the extracts from organs obtained from other animals. The nature of the poisons contained in them did not appear to differ."

The following conclusions appear warranted:—

1. *Removal of both adrenals arrests the supply of a secretion which these organs pour into the adrenals.*

2. *The secretion of the adrenals gives rise to physiological phenomena which are not awakened by extracts of other organs.*

^{32a} Swale Vincent: "Internal Secretion and the Ductless Glands," p. 232, 1913.

³³ Cybulski: *Loc. cit.*

³⁴ Mankowsky: *Russian Archives of Physiology and Bact.*, March, 1898.

³⁵ Guinard and Martin: *Journal de physiologie et de path. génér.*, 1899; *Archives générales de médecine*, Oct., 1899.

EFFECTS OF THE ADRENAL SECRETION ON THE CARDIO-VASCULAR SYSTEM.

THE ADRENAL SECRETION AND THE CARDIAC MUSCLE.—While removal of both adrenals is followed by a great fall of blood-pressure and very feeble and rapid cardiac action, intravenous injections of suprarenal extract invariably cause marked increase of the blood-pressure and equally marked slowing of the heart-beat. The blood-pressure increase thus appears to be due to the direct effect of the specific suprarenal principle; but to account for the slowing of cardiac action we are led to implicate the inhibitory action of the vagus. If the bulbar center of this nerve be paralyzed by atropine, however, or the vagus itself be cut, this inhibition ceases and quickening of the heart-beat follows, accompanied by a still greater increase of blood-pressure. Oliver and Schäfer found³⁶ that the inhibitory action of the vagus under the influence of adrenal extract was sufficient to arrest the auricles for a time, the ventricles continuing to contract slowly.

Mooted points have arisen in this connection that have entailed considerable divergence among physiologists; and, curiously enough, when the various views entertained are analyzed, none of them seem to harmonize with available experimental data.

Cybulski,³⁷ after a series of careful experiments, reached the conclusion that suprarenal extract acted upon the vasomotor centers of the medulla and spinal cord, first stimulating, then paralyzing, them. Oliver and Schäfer,³⁸ after equally careful experiments, concluded that the extract caused powerful constriction of the arterioles by a direct action on their walls, and stimulated the inhibitory center. To this they ascribed the slowing of the heart observed before the vagi were cut, and physiologists have generally accepted the conclusion that the inhibitory center is stimulated. Indeed, even the more recent—and carefully conducted—physiological researches have sustained this opinion; Wallace and Mogk,³⁹ for instance, were

³⁶ Oliver and Schäfer: *Journal of Physiology*, xviii, 1895.

³⁷ Cybulski: *Gazeta Lekarska*, March 23, 1895.

³⁸ Oliver and Schäfer: *Journal of Physiology*, vol. xviii, p. 230.

³⁹ Wallace and Mogk: *American Physiological Society Proc.*, Dec. 28, 1898.

led by unquestionable experiments to conclude that the suprarenal extract stimulated the vagus center, thus inhibiting the heart.

A second set of divergent views refers to the nervous structures involved when the heart is separated from its inhibitory center by section of the vagus. The influence of the extract, in this connection, is ascribed by Mankowsky⁴⁰ to stimulation of the cardiac and respiratory centers; by Gottlieb,⁴¹ to the direct stimulating effects of the substance upon the intrinsic cardiac ganglia; by de Cyon,⁴² to some action upon the vasoconstrictor nerves and simultaneously upon the central and peripheral ends of the cardiac accelerators; by Velich,⁴³ to stimulation of the vasoconstrictors; and finally by other observers to various more or less complicated combinations which all include some part of the nervous system as the seat of primary effect. By inference, therefore, we are led to look upon this system as the one upon which the specific principle of the adrenals acts physiologically.

A leading question, which embodies the divergent views of Cybulski, on the one side, and Oliver and Schäfer, on the other, resolves itself into this: Does the suprarenal active principle act at all upon the inhibitory centers?

It may prove useful in this connection to recall that, according to prevailing doctrines, the functions of the heart are governed by two sets of nerve-fibers. The one set, derived from the sympathetic, increases the vigor of the heart-beat and tends to quicken the number of beats in a given time. The other set, which arises from the vagus, inhibits the vigor of the heart-beats and their rate or rhythm. Both these "augmentor" and "inhibitor" fibers receive their impulses from the medulla oblongata and from a limited area of the upper portion of the cord, and represent the external, or extrinsic, motor-supply of the organ. Again, the medulla and the spinal area referred to receive impulses—including reflex impulses—from all parts of the organism, including the heart proper, and there is thus

⁴⁰ Mankowsky: Russian Archives of Pathology, Clinical Med., and Bact., vol. v, No. 3, March, 1898.

⁴¹ Gottlieb: Archiv für exp. Path., Bd. xxxviii, 1896.

⁴² De Cyon: Pflüger's Archiv für Physiol., vol. lxi, p. 370, 1898.

⁴³ Velich: Wiener med. Blätter, Nov. 11, 1897.

established a cycle of afferent and efferent impulses of which the medulla and the portion of the cord immediately below it represent the center. The effects of destruction of these structures can easily be foretold. As shown by Stricker nearly forty years ago and by other physiologists since, extirpation of the cervical and dorsal portions of the cord causes arrest of the heart's action. When to this is added destruction of the medulla, the certainty of immediate death is but enhanced. Again, certain agents—chloral hydrate, for instance—are known to abolish the functional activity of the cord and to affect the heart as if the vagus had been severed.

Applying these classical data to the question in point, it becomes evident that, if the inhibitor or augmentor centers were directly or reflexly stimulated by suprarenal extract, the effects of extirpation of these centers or of the cord would not be counteracted by its use *since there would be no center to receive and transmit impulses*. The arrest of the heart's action would therefore be permanent.

But experiments have shown that the injection of suprarenal extract at once causes this organ to resume its beat notwithstanding total extirpation of the entire cord. Thus, Biedl⁴⁴ cut the medulla oblongata and removed the entire cord of mammals; and, when the blood-pressure had become reduced to 9 millimeters, injected suprarenal extract. This at once brought up the pressure to 160 millimeters. Gottlieb⁴⁵ chloralized rabbits until the heart-beats became irregular and excessively slow. An injection of suprarenal extract at once restored the regularity and volume of the pulse. He tried the same experiment when the pulse was no longer registrable by the manometer; a similar result was obtained, and the heart almost immediately resumed its normal action. Isaac Ott⁴⁶ etherized a rabbit, cut the cord above the atlas, severed all the cardiac nerves in the neck, and verified the section of the cord *post mortem*. Injections of suprarenal extract were then used repeatedly as soon as the pressure became greatly lowered. They brought it up from 24 to 144 the first time, from 17 to

⁴⁴ Biedl: Wiener klin. Wochenschrift, Bd. ix, 1896.

⁴⁵ Gottlieb: Archiv für exp. Path. und Phar., Bd. xxxviii, 1896.

⁴⁶ Isaac Ott: Experiment No. 11, Medical Bulletin, Jan., 1898.

134 the second, and from 24 to 124 the third time, the interval between the injections of extract and the highest-pressure marks ranging from fifteen to thirty seconds.

These experiments, to which others of a similar kind could be added, speak for themselves. They distinctly show that, contrary to the conclusions of Cybulski, Wallace and Mogk, Man-kowsky, Gottlieb, and other observers, *the inhibitory centers are not directly stimulated by the suprarenal extract.*

And, indeed, their conclusion is apparently justified, if removal of the medulla and cord is left out of consideration, and with injections of suprarenal extract as an only guide. In other words, to the question—does suprarenal extract directly affect the cardio-inhibitory centers?—an affirmative experimental result on injecting it into mammals—slowing of the heart—would always be obtained, while the crucial test—section of the vagus—would at once confirm the conclusions previously reached by causing great increase in the rapidity of the heart's action. But division of the cardiac nerves in the neck, including the vagus, and of the cord in no way preventing the action of the extract, the only logical deduction that imposes itself is that *the suprarenal extract exercises a stimulating action directly upon the cardiac muscle irrespective of any action upon the inhibitory centers.*

THE ADRENAL SECRETION AS CONSTRICTOR OF MUSCULAR ELEMENTS.—The last deduction implicates other phases of the question. Prominent among these is the effect ascribed to suprarenal extract upon the vasomotor system by various physiologists and clinicians. Is there any such action? Veins—which are but little, if at all, influenced by the cardiac impulse in respect to their rhythmical changes of caliber, the blood before reaching them having to penetrate the capillary system—are distinctly contractile. This may be clearly seen by examining the great veins opening into the heart, and in those of bat's wings. “Although,” to use Foster’s⁴⁷ words, “similar rhythmical variations, also possibly due to rhythmical contractions, but possibly also of an entirely passive nature, have been observed in the portal veins, very little is known of any nervous arrangements governing the veins.” Granting that veins

⁴⁷ Foster: “Text-book of Physiology,” 1895.

are not endowed with a vasomotor supply, we find that they nevertheless contract under the influence of suprarenal extract. Szymonowicz⁴⁸ observed that the pressure rose and fell in the external jugular vein, along with the pressure caused in the arteries by injections of this substance. Auld⁴⁹ states that, when suprarenal extract was injected into a vein "which had been clamped as high as practicable, on releasing the vein after a few minutes a marked diminution of pressure was recorded as compared with that produced by injection into the free vein." This shows a direct action on the vein while the extract was held *in situ* by clamping. While it is difficult to account for the *general* increase of vascular pressure caused by the extract without including vasomotor nerves in the process, a direct action upon the vascular muscles themselves *might* underlie the result attained: a question which can only be elucidated by stripping the vessels of all their nervous connections and then watching the effects of the extracts. This procedure has been resorted to by Oliver and Schäfer,⁵⁰ and these physiologists have shown that a vessel will contract after all the nerves to it are cut. Even a freshly excised vessel—one, therefore, obviously freed of all nervous influence—will respond to the contracting effects of an aqueous solution of suprarenal extract, and, if a large vessel be used for the experiment to render the change of caliber more appreciable, the diameter will be found reduced nearly one-sixth. Furthermore, these investigators⁵¹ have found that it acts directly on the muscles of the blood-vessels, and that this action occurs equally well *after section of the cord*. As we have seen, destruction of the adrenals or annihilation of their functions is followed by extreme muscular weakness; this normally led them to the conclusion that all varieties of muscle—the striated, non-striated, and the cardiac muscle (which histologically partakes of both kinds of muscular tissue)—are stimulated by the extract.

Observing also that the latter caused a rapid increase of blood-pressure, and that it gave a steep rise to the kymograph-

⁴⁸ Szymonowicz: *Archiv für die gesam. Physiol.*, Bd. lxiv, 1896.

⁴⁹ Auld: *British Medical Journal*, June 3, 1899.

⁵⁰ Oliver and Schäfer: *Journal of Physiology*, vol. xviii, p. 426.

⁵¹ *Ibid.*, p. 230.

curve, they concluded that there had been a strong constriction of the small arteries: strong, in their sense, meaning the relative constriction as compared to that of other vessels. This is fully accounted for by the greater relative supply of muscular tissue in these peripheral vessels. As is well known, arteries are endowed with a coat of muscular fibers, which assumes increased thickness and relatively greater mechanical power as the capillaries are approached; so that in the smaller arteries the muscular layer is relatively quite thick. All the work done in recent years has emphasized the fact that the adrenal active principle enhances the tone of blood-vessels, chiefly that of the *arterioles*.^{51a} though not of the coronaries or pulmonary vessels.

That all organs are similarly affected owing to their vascular supply was also shown by Oliver and Schäfer by means of the plethysmograph, not alone the limbs, but such organs as the spleen and the kidney being contracted from 20 to 25 per cent. after intravenous injections of the extract. These experiments also showed that great vascular constriction in the splanchnic area was caused. Veins, we have seen, are likewise constricted by suprarenal extract; they also contain muscular fibers in their thinner walls. Although the supply of muscular elements is less important than in the arteries, this is, to a degree, compensated by the greater lumen. That the entire vascular system of the organism is thus acted upon by the suprarenal specific principle, owing to the muscular tissues which it contains, is beyond question.

Can we conclude from these data that the vasomotor center is never influenced by the suprarenal extract? As will be shown later on, the secretion of the adrenals and adrenal extractives enhance metabolic activity in living cells, including vascular elements. Their action on vessels is thus independent of any upon the vasomotor center except in so far as their influence on general metabolism is concerned, in which case this center would merely be stimulated along with all other tissues.

Briefly, Schäfer's statement that "the intravenous injection of suprarenal extract produces a powerful physiological action upon the muscular system in general, but especially upon the muscular walls of the blood-vessels, and the muscular wall of the

^{51a} Swale Vincent: "Internal Secretions and the Ductless Glands," p. 164, 1913.

heart" may be accepted as the basis of the conclusion that *suprarenal extract causes cardiac and vascular contraction by stimulating directly the muscular elements of the heart and vessels, and mainly the arterioles.*

ACTION OF THE ADRENAL SECRETION UPON THE HEART.

—The addition of a given proportion of glandular substance to the aggregate contained in the organism, or the removal of some by any method, should involve a corresponding augmentation or a diminution of the normal manifestations that represent suprarenal functions, whatever these may be. The injection of suprarenal extract, we have seen, produces a rapid and marked increase of blood-pressure. When, therefore, we speak of stimulating these structures we imply contraction of the muscular fibers and approximation of the vascular walls toward the center of the blood-stream and as a corollary, increased tension in the veins, with resistance to, and slowing of, the contractions of the right ventricle. Biedl^{51b} states in this connection: "The full action of adrenalin may, however, be observed in the mammalian heart *in situ* after the vagal terminals have been paralyzed with atropine. There is, as a rule, a further acceleration of the contractions and there is, especially, a stronger ventricular systole which is well seen by registering the contractions or by means of a plethysmograph. This increased cardiac activity is the result, not of improved circulatory conditions arising out of the heightened blood-pressure, but of the direct action upon the heart of the substance itself. Thus, the intravenous injection of suprarenal extract will bring back life into an animal poisoned with chloral, in which the action of the heart is almost or entirely obliterated. The injection is followed by a progressive increase in the rapidity and *power* of the contractions; the blood-pressure, which had fallen to nothing, rises; and, after a second injection, the heart resumes its normal activity which is maintained. . . . The action of adrenalin may also be observed in hearts which have been removed from the living body. Oliver and Schäfer experimented with isolated frogs' hearts through which normal saline solution was allowed to circulate. They found that suprarenal extract produces spontaneous contraction in a motionless heart; in the case of a feebly

^{51b} Biedl: "Internal Secretory Organs," p. 200, 1913.

beating heart, the beats become stronger and more rapid, the irregularity disappears, and rhythm is restored. . . . Hering-Bock found that an increase in the pulse-rate and a stronger cardiac contraction also followed the employment of adrenalin in the isolated cardiopulmonary circulation." Briefly, these facts, which summarize the observations of a larger number of experimenters clearly show that *an excess of adrenal extract in the blood increases the contractile power of the cardiovascular system.*

Under these conditions, it seems evident that the blood tends to gravitate toward the periphery.

FUNCTIONAL RELATIONSHIP BETWEEN ARTERIES AND THEIR CAPILLARIES UNDER THE INFLUENCE OF THE ADRENAL SECRETION.—The very marked contractile power that suprarenal extract also possesses over the cardio-vascular muscles plays an important indirect rôle in the organism which seems to have been overlooked so far: *i.e.*, that, *since capillaries are not supplied with muscles (their walls consisting of endothelial plates), they are not contracted as are arteries and arterioles.*

This embodies two kindred prominent features of pathology: *i.e.*, the fact that *when vessels supplied with a muscular coat contract their capillaries dilate* owing to the increased pressure to which the arterial contraction gives rise within the latter, while the opposite relative mechanism—*when vessels supplied with a muscular coat dilate their capillaries contract*—prevails owing to the resiliency of the latter when the blood in them recedes. In other words, while, in the first case, the blood is crowded outwardly, in the second it is crowded inwardly.

The physiological importance of these propositions will be shown in subsequent chapters, but their bearing and soundness seem sustained by the fact that they alone, of all solutions so far advanced, can satisfactorily explain an experimental phenomenon—a true suprarenal paradox—encountered by Langlois and Charrin in the course of their earlier laboratory work.⁵² These observers, in order to study the action of suprarenal substance upon toxic agents and toxins, injected equal doses of virulent cultures into two groups of guinea-pigs, the animals constituting one of the groups having each been deprived of one suprarenal gland. The group of *normal* animals

⁵² Langlois and Charrin: *Comptes-rendus de la Société de Biologie*, July 10, 1896.

lived altogether 138 hours,* that of *mutilated* animals 150 hours. Several experiments of the same kind were performed; invariably did they find that the animals from which one gland had been extirpated lived longer than those left in their normal condition. The differential contractility of vessels and capillaries referred to render this phenomenon a normal consequence under the circumstances: The caliber of the *muscular* vessels, veins, and arteries of the mutilated animals having become enlarged and their walls relaxed by the loss of suprarenal stimulus, engorgement of the larger trunks occurred, and caused *depletion of the remote capillaries*, including those of the central nervous system. The virulent toxins injected producing their main primary effects upon the latter, and, the quantity of toxic blood transported to them in a given time being smaller than in a normal animal, the longevity of the latter was prolonged in proportion.

I shall frequently refer in subsequent chapters to this relative behavior of vessels under the effects of suprarenal secretion or extract. We will see also that it is an important feature, not only of the physiological action of certain drugs, but also of various toxins, that of the pneumonia bacillus, for example. The conclusion, therefore, that *vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation* is only submitted as a postulate for the time being.

TOXINS, POISONS, VENOMS, AND DRUGS IN LARGE DOSES AS INHIBITORS OF ADRENAL FUNCTIONS.

Analogy suggests that, besides the normal standard of suprarenal activity, there must be inadequate activity, physiological to a certain extent, but pathological when extremes are approached. Pending considerable testimony to this effect it is sufficient to recall that insufficiency of the adrenals is now recognized as a clinical entity. We have seen that hemorrhage into both adrenals can cause death, and we shall see presently that various poisons likewise cause, mainly by variations of the blood-pressure, cessation of the adrenal functions. Is this result due to direct annihilation of the latter by the poison, or must

it be ascribed to some indirect factor, such as the variations of general blood-pressure, caused, as is well known, by many poisons, including certain toxins, and which must necessarily affect the adrenals as well as other organs?

This question may perhaps be elucidated by trying to account for the hæmorrhages that occur as a complication of local disease. These at first seem to afford a ready answer, since the vast majority of them are traceable to organic lesions of the glands that practically annul their efficiency by destroying the greater part of their substance. Partial destruction of the organs and corresponding loss of activity follow each other so logically that any conclusion other than that, in accord with the prevailing view, all poisons, toxins especially, act morbidly upon the adrenal tissues *per se* would seem unwarranted. And yet we have in cerebral hæmorrhage or "apoplexy" evidence to the effect that adrenal hæmorrhage, which Arnaud termed "adrenal apoplexy," might also be due to high general blood-pressure, with rupture of the adrenal vessels, particularly when these vessels are diseased. Again, poisons being carried to all parts of the organ we should, if their action were direct, find the lesion in the functional cellular elements throughout the entire organs. Not only is this not the case, but the lesions are essentially vascular.

While studying the pathological histology of suprarenal hæmorrhage, Arnaud found that it was not in the medulla proper, as generally believed, that these hæmorrhages occurred, but in the tissues of the internal cortical zone. In emphasizing this fact, he states: "It is at this point that the *capillaries tear under the influence of a powerful congestion*. When the hæmorrhage is important, it is due to *rupture of one of the branches of the capsular vein* at any point of its walls, and occurs into the medullary substance or into the central conjunctivo-vascular sheath." The medulla proper may be respected to the last, either a capillary peripheral to it, or some part of the intrinsic portion of the vein—probably weakened by the local disease—constituting the yielding structure. Furthermore, Nature seems to protect the last vestiges of the medullary substance even after a localized hæmorrhage. This is suggested by the fact that Arnaud found in such areas evi-

dent signs of organization, at times indicating a local interstitial inflammatory process, at others a retrogressive metamorphosis recalling that observed in hæmatomata. Briefly, using his words: "The normal anatomical elements of the suprarenal gland may be found in a more or less perfect state of integrity, either in the periphery of the growth or at one of its extremities." Toxins would hardly be so selective.

Further analysis of this question elicits the fact that the symptoms which characterize the progress of the primary organic disease of the adrenals differ totally from those attending the hæmorrhage proper. While the former may hardly cause suffering or be totally obscured by the signs of any concomitant disorder present, the symptoms attending hæmorrhage are particularly violent and sudden, the patient abruptly screaming from excruciatingly intense pain in the abdomen, or dropping at once into apoplectiform coma from which he never rallies. Cerebral apoplexy does not furnish a more vivid picture of the overwhelming effects of hæmorrhage. Yet hæmorrhagic foci in various stages of organization are found at autopsies. Thus, one of Arnaud's cases suddenly fell into apoplectiform coma, and died in 48 hours; the only organs found diseased after death were the adrenals, which contained old hæmatomata, and various more or less organized hæmorrhagic foci which showed that local hæmorrhages into them had repeatedly occurred. The suprarenal substance was entirely destroyed excepting a narrow zone toward the inferior edge of the right organ. The urine, during life, and the kidneys, after death, were found normal. Obviously we cannot well ascribe the acute symptoms to the primary organic lesion, since they appear suddenly, practically without warning, and promptly lead to a fatal issue. Excessive, *i.e.*, disruptive congestion again suggests itself.

Confirmatory evidence is also afforded by the facts that, irrespective of infectious diseases, adrenal hæmorrhage may be caused by cardiac and renal disorders in which high blood-pressure results from purely mechanical causes, and that, as is often the case, fatal adrenal hæmorrhage may occur irrespective of any evidence of local disease or the presence of any bacteria. This is well shown in Andrewe's case, referred to on page 6, in which

neither cultures nor stains showed the presence of pathogenic organisms.

There is good ground for the belief, therefore, that the prevailing view that poisons act directly upon the adrenal tissues does not always apply, *i.e.*, that, *besides the insufficiency of the adrenals caused by disease of these organs, there is a form brought on by the general blood-pressure when this is sufficiently elevated (as in the course of some infections and intoxications) to cause intense congestion of the adrenals and rupture of some of their blood-vessels.*

The morbid influence of high blood-pressure is all the more likely to manifest itself when part of the adrenals have already been destroyed by local disease—since the disruptive pressure is concentrated upon a smaller number of vessels—or when lesions of the vessels, atheroma, for instance, have diminished their power to resist centrifugal pressure. Important in this connection, however, is the fact that, contrary also to the prevailing opinion, there is ground for the belief that hypertrophy of the adrenal secretory tissues, which has been observed by Langlois, Charrin, Petit, Stilling, and others in animals (see page 36) under the influence of injected poisons, does not appear to exert any compensative influence when local disease has destroyed any part of the medullary zone of the gland.

As shown by Langlois, Gourfein, and others, mammals continue to live, when all but one-eleventh of their adrenals had been extirpated—or destroyed by cautery or disease we might add — that, unless some compensative action or some accessory organ be present, death occurs when this limit of normal adrenal substance is reached. It seems logical, therefore, that, were the medulla itself capable of assuming compensatory activity, so large a supply for emergencies (the nature of which will be described later on) would hardly have been provided. If analogy be again accepted as guide, other organs do not compensate for what insufficiency organic disease may produce in them by overtaxing remaining normal structures; collateral chromaffin tissues, supernumerary or accessory organs, vicarious functions, and hypertrophy being all *added* elements, thus constituting either auxiliary resources *per se* or auxiliary resources *plus* compensative growth. Even in the case of the organs

of special sense, where the loss of one organ imposes all the physiological labor upon the other, the existing tissues are not overtaxed; they are brought to their highest proficiency by the increase of nutrition which the additional functional use involves. Whatever evidence we have, therefore, tends to show that the *remaining normal structures of a diseased adrenal are not replaced by new adrenal tissue, and that they are increasingly exposed to disruptive congestion as the local morbid process advances.*

It is because of this that adrenal hæmorrhage is observed with relative frequency in Addison's disease. Moreover, Labazine⁵³ found experimentally that lesions of the adrenals showed that these organs possessed very little regenerative power. When large portions of the glands were excised no restoration of parenchyma occurred.

TOXICS WHICH PRODUCE CONGESTION OR VENOUS STASIS IN THE ADRENALS.—The list of disorders to which adrenal hæmorrhage has been attributed is steadily increasing. Pneumonia, diphtheria, thrush, variola, scarlatina, tuberculosis, meningitis, cancer, septicæmia, purpura, uræmia, asphyxia (toxic wastes), burns (toxic wastes and detritus), typhoid, jaundice and eclampsia seem, however, to stand out most prominently—all of which present as militant agent either a toxin or some toxic intermediate waste. The effect of burns is illustrated by Arnaud's case, in which sudden death followed a burn of the arm. Andrewes's case, in which death occurred 36 hours after the first symptoms of an acute disease which he thought bore some points of resemblance to hæmorrhagic small-pox, also illustrates this class. In fact, instances such as Andrewes's have so often been noticed by clinicians that Still⁵⁴ has proposed a distinct category of cases in which "after an acute illness lasting only two or three days, usually with a purpuric or bullous eruption," death occurs, "and the suprarenal lesion appears to be a part of the fatal issue."

That general intoxication can thus act as an original cause of hæmorrhage has been shown experimentally. Thus, Roger⁵⁵

⁵³ Labazine: Arch. des Sciences Biologiques de St. Petersburg, p. 249, vol. xi, 1905.

⁵⁴ Still: Lancet, May 7, 1898.

⁵⁵ Roger: Berliner klin. Wochenschrift, Jan. 21, 1894.

found that inoculation of the guinea-pig with a culture of the pneumobacillus of Friedländer was followed by profuse hæmorrhage into both capsules, the blood actually bursting through the great capsular vein, or causing necrosis of the surrounding elements by mechanical compression. Langlois⁵⁶ also demonstrated that suprarenal hæmorrhage could be brought on by the bacillus pyocyaneus. Charrin⁵⁷ found that, by injecting diphtheria toxins into guinea-pigs, congestion—which in some instances reached the hæmorrhagic stage—was not alone caused, but he also observed that small doses used repeatedly and during prolonged periods caused hypertrophy of the organs. Petit⁵⁸ also noted, after introducing Löffler bacilli in fishes in which the suprarenal structure is clearly glandular, that all the phases of excessive reaction could be brought on. Hæmorrhagic foci were found by Wybauw⁵⁹ in the adrenals of a child which had died of broncho-pneumonia the result of a tracheotomy for croup. Kiesmann found the staphylococcus aureus and albus, and Hamill and Dudgeon the pneumococcus.

That the functions of the adrenals are actually inhibited by these various pathogenic agencies has been shown in various ways. Mott and Halliburton, for example, found that after death from exhausting diseases the proportion of active principle present in the adrenals was either absent or greatly reduced. By ascertaining the relative proportion of chromaffin granules in the adrenals of 50 adults who had died of various diseases. Bainbridge and Parkinson⁶⁰ were able to note the absence of the agent in the medulla of the organs of cases which had died of infectious diseases, peritonitis, shock, or where a low blood-pressure had existed. Luksch^{60a} ascertained the degree of functional disturbance caused in the adrenals by disease, by ascertaining the relative pressure-raising power of their extracts. While certain conditions, starvation, simple fever, did not show any material change in this direction, various infectious diseases, uræmia and phosphorus poisoning, caused the extracts not to display the normal pressure-raising property.

⁵⁶ Langlois: *Le Bulletin Médical*, Feb. 7, 1894.

⁵⁷ Charrin: *La Semaine Médicale*, June 3, 1896.

⁵⁸ Petit: *La Semaine Médicale*, June 3, 1895.

⁵⁹ Wybauw: *Annales de la Société Royale des Sciences Méd. et Nat. de Bruxelles*, vol. vi, Nos. 2 and 3, 1897.

⁶⁰ Bainbridge and Parkinson: *British Med. Jour.*, May 11, 1907.

^{60a} Luksch: *Wiener klinische Wochenschrift*, B. xvii, No. 14, April 6, 1905.

Of course, a certain proportion of these cases may be attributed to exhaustion of the glands during the course of the disease. That the morbid effects are mainly due to excessive variations of the blood-pressure is suggested by the location of the organs, the richness of its blood-vessels, especially of its veins, the proximity of the inferior vena cava, which receives the blood almost directly from the gland on the right side. Pressure during labor upon the inferior vena cava and the suprarenal gland, located, as they are, between the liver anteriorly and the vertebral column posteriorly, may also give rise to congestion of the vessels of the glands and result in hæmorrhage.

Various drugs may bring on hyperæmia, congestion, and hæmorrhage of the suprarenal glands, as shown by Pilliet,^{60b} who observed these phenomena after the use of nitrate of uranium. Essence of cloves has also been found capable of stimulating them to such a degree as to bring on macroscopically visible lesions.

On the whole, the conclusion seems warranted that *so many toxic substances cause adrenal hæmorrhage that a common effect of all these poisons on the general blood-pressure, sufficient to cause active or passive congestion or venous stasis in the adrenals, is necessary to explain the genesis of this class of cases.*

INCREASED FUNCTIONAL ACTIVITY OF THE ADRENALS AS A PREDISPOSING CAUSE OF ADRENAL HÆMORRHAGE.—The view that the adrenal specific principle itself possesses antitoxic powers has suggested to those who have accepted it the conclusion that a high degree of toxæmia, by overtaxing the organs, caused congestion, and, if this reached beyond certain limits, hæmorrhage. This conception was mainly based on the view of Brown-Séquard, who was led, by the toxic effects of blood taken from decapsulated animals upon normal ones, to ascribe to the *glands themselves* a direct antitoxic function. It met with further support in the fact that violent toxæmia invariably follows the removal of both organs, and was therefore accepted by many investigators. It was also maintained by Dubois,⁶¹ who, having isolated toxic alkaloids from adrenal substance identical in some of their reactions with muscle-toxins, concluded

^{60b} Pilliet: Le Bulletin Médical, Feb. 7, 1894.

⁶¹ Dubois: Archives de Physiologie norm. et path., vol. viii, 1896.

that the adrenals occluded products of organic waste and modified them *in situ*, but that they did not seem to secrete any special substance destined to enter the circulation. This view has not withstood any degree of close scrutiny. The destruction of poisons *within* the adrenals themselves involves the passage of the systemic blood through their cellular elements. When in the cadaver we note the relative dimensions of all the vessels within a narrow radius of the adrenals, it becomes apparent that the conditions are not such as to indicate a provision for the passage of the blood through these organs. Moreover, if the adrenals were intended to destroy toxics in the blood traversing them, the afferent channels would normally contain blood from all parts of the organism and charged with toxic elements, while the efferent channels would convey the purified blood charged with the suprarenal secretion to the heart, ready for redistribution. Instead of this the afferent vessels receive their blood from the aorta,—arterial blood,—while the efferent vessels pour their blood into the vena cava. But, as shown by Alezais and Arnaud⁶² in 1890, this blood is *also arterial*. We thus have a short arterial circuit, or loop, which, besides furnishing the adrenals their intrinsic and functional blood-supply, evidently has for its purpose the immediate return to the general circulation of a small quantity of arterial blood charged with what Claude Bernard (1867) has well termed an “internal secretion.”

More in keeping with experimentally established facts are the views which attribute to the secretion itself, when in the blood-stream, the antitoxic functions referred to. Thus, Abelous and Langlois,⁶³ after a series of careful experiments, reached the conclusion that their normal function was to elaborate an internal secretion capable of neutralizing or destroying the poisonous substances resulting from muscular contractions: a fact further demonstrated to them by the mitigating effects of injected suprarenal extract. Some years later these observers⁶⁴ amplified their views and concluded that, after removal of both adrenals, there was a true auto-intoxication, the animals generating poisons which were normally

⁶² Alezais and Arnaud: Quoted by Arnaud, *loc. cit.*, p. 34.

⁶³ Abelous and Langlois: *Archives de Physiologie norm. et path.*, vol. III, p. 267, 1892.

⁶⁴ Abelous and Langlois: “Travaux de Laboratoire,” *Lancet*, Aug. 20, 1898.

either destroyed or changed in the interior of the glands or by material formed by the organs and poured into the blood. The poisons, they thought, were probably products of muscular activity and also of bacterial origin, and exerted a special influence on the heart and circulatory system. Mosse⁶⁵ also believed that the adrenals produced a stimulating substance and that they could simultaneously neutralize poisons formed in various parts of the organism.

Reasoning by analogy, we can surmise that the metabolism of the organs is principally maintained by the passage of blood through them and that the internal secretion represents the physiological product of their metabolism. Under these circumstances, the quantity of blood in them at a given time would stand as the controlling factor, the quantity of active principle secreted into the general circulation being proportionate to this quantity. Have we any ground for the belief that the circulation alone may keep up the suprarenal functions? The experiments of Soddu⁶⁶ seem to throw light upon this question. In order to ascertain the rôle of the suprarenal peripheral nerves, this investigator isolated the glands of several dogs from their external connections, leaving only the blood-vessels. Although eight animals were submitted to this operation, none died, and all, after a few days, were in their normal health. It is evident that, if the blood alone can thus sustain the life of the organs, an increased flow into them—under, perhaps, the influence of toxic blood upon the centers of their nerve-supply—will involve a corresponding increase of functional activity. That very large or overwhelming doses of any poisonous agency should produce the contrary effect and arrest the functions of the adrenals by annihilating those of their center is suggested by the pathogenesis of suprarenal hæmorrhage.

Still, this involves the existence of an intrinsic nervous supply capable of producing an increased flow of blood into the glands under the stress of an acute toxæmia and a corresponding increase of vascular tension. By suddenly calling the suprarenal functions into violent activity, an excessive dose

⁶⁵ Mosse: *Fortschritte der Medicin*, No. 21, 1897.

⁶⁶ Soddu: *Lo Sperimentale*, No. 2, 1898.

would thus paralyze them or cause what Arnaud has termed "suprarenal apoplexy": *i.e.*, intrinsic hæmorrhage. To ascertain whether such a nervous influence can exist, and, if it does, whether a poison can stimulate the glands through the latter's nerve-supply, is necessary before further progress can be made.

Biedl⁶⁷ studied the effects of various poisons, particularly atropine, to ascertain whether they influenced the character or quantity of suprarenal secretion, and obtained negative results. But can this be said to apply to *all* poisons? A close analysis of this physiologist's work has led me to interpret his experiments in a manner that is not in accord with his conclusion. He states that he found blood-pressure to be increased in the organ by the interruption of artificial respiration. This interruption appears to me to point to an accumulation in the organism of *products of metabolism*, and therefore of poisons of a class which stand out prominently as the basis of phenomena that promptly end in death. That products of metabolism may with justice be considered as toxic is shown by a detail in Langlois's work, the importance of which does not seem to have attracted sufficient attention: While decapsulated frogs died in 48 hours during summer months, they lived 12 days in the winter, *i.e.*, during hibernation, when metabolic processes are at their lowest ebb. It required a certain ratio of toxic elements to the body-weight to bring on the culminating phenomena; the "fatal dose" was made up in 48 hours, in summer,—*i.e.*, when the full activity and proportionate catabolism prevailed; the same relative dose could only be made up in six times 48 hours when hibernal lethargy reduced tissue-waste in proportion. Thus, Biedl's experiments are not negative in this direction, as he deemed them to be. They appear to me to suggest that, as will be shown in these pages, all toxics do not influence the adrenals with equally marked activity.

Biedl also found that, when the splanchnic nerve was cut and the suprarenal branches were stimulated, hyperæmia appeared in the organs. Howell refers to the striking evidence afforded by the effects of electrical stimulation. If, after cutting the splanchnic nerve and introducing a cannula into the suprarenal vein, the blood is collected and the peripheral end

⁶⁷ Biedl: *Pflüger's Archiv*, vol. lxxvii, H. 9 and 10, 1897.

of the cut nerve is stimulated, the quantity of blood obtained in a definite time is not increased, but it is found to contain more of the blood-pressure-raising substance: a fact which indicates that its secretory activity is increased. He therefore concludes that the adrenals act as true glands, and that they are provided with a reflex mechanism corresponding to that of the latter. Biedl also expressed his conviction that secretory fibers as well as vasodilator fibers are present in the splanchnic nerves. Dogiel⁶⁸ likewise found that the medullary nerves form complicated plexiform arrangements which terminate upon the surface of the glandular elements, and, furthermore, that the nerve-cells in no way differ from those of any sympathetic ganglion.

This experiment tends to show, and additional labors have only served to emphasize their soundness, that the functions of the adrenals are governed by the splanchnic nerve. We are thus brought to conclude that, in keeping with many important functions, those of the adrenals are regulated by some center (which I will describe farther on) somewhere in the cerebro-spinal axis. Again, we learn that stimulation of this nerve increases the functional activity of the adrenals *without* increasing the volume of blood given out by the gland *with* the secretion. But as shown by Claude Bernard, it is by augmenting the blood supplied to a gland that its functions are enhanced; and it happens also that it is not in the secreting elements that the hæmorrhages into the adrenals occur, but mainly in the cortical zone. This indicates that the blood-streams which serve to increase the secretory activity organs do not yield their blood through the vessels which transfer the adrenal secretion to the inferior vena cava. We have such vessels—which, unlike the veins to the latter, carry venous blood—in the many veins which the adrenals send to the renal veins.

The bulk of evidence, therefore, tends to show that *increased functional activity of the adrenals being attended by an increased supply of blood to these organs, it must be considered among the predisposing causes of adrenal hæmorrhage.*

But we have seen also that the splanchnic contains the secretory nerves to the adrenals, and that this implicates the

⁶⁸ Dogiel: Archiv f. Anatomie und Physiologie, p. 90, 1894.

existence of some governing center for these organs. When we add to this the antitoxic properties of the adrenal secretion, it appears possible at least that *it is partly by exciting the adrenal center that various poisons predispose the adrenals to hæmorrhage*, the purpose being, as we shall see, to augment the antitoxic power of the blood.

PASSIVE CONGESTION OF THE ADRENALS BY TOXICS WHICH DEPRESS THE BLOOD-PRESSURE.—Oliver and Schäfer, by plethysmographic observations upon the limbs and spleen, found that injections of suprarenal extract produced great vascular constriction, chiefly in the splanchnic area. That deficiency of suprarenal secretion in the organism should produce the opposite result in the same region is shown by the fact that removal of the adrenals is followed by relaxation of the same great vascular channels.

This central engorgement of suprarenal origin—greatly accentuated through the fact that “vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation”—seems far reaching in its application. The symptoms of acute arsenic poisoning will serve to illustrate this fact.

As a result of the central accumulation of blood, the extremities and peripheral tissues, more or less depleted of theirs, are cold; the muscles, also deprived of the greater part of their blood, lose their power; the tension upon the abdominal vessels and neighboring structures, including the unusually rich nervous net-works, produces the intense abdominal pain; engorgement of the intestinal vessels gives rise to copious diarrhœa, which by causing reduction of liquids tends to reduce the renal secretion and sometimes to cause anuria. The depletion of the cerebral vessels accounts for the syncope, and the auto-intoxication, through accumulation of waste-products, for the convulsions. These phenomena recall so clearly the symptoms that follow removal of the adrenals that we cannot but suspect that arsenic must in some way arrest the functions of these organs.

Still, while the various morbid conditions outlined account for the symptoms recorded, closer investigation soon shows that they are only satisfactory as far as they go, and that some features of the symptom-complex are not fully met. Thus,

general relaxation of the vascular system means sudden increase of caliber of all vessels, and, therefore, a corresponding increase of area for the blood. Why should it, under these circumstances, accumulate in the larger trunks? Why should it not merely lie dormant in the relaxed vessels evenly distributed throughout them all? Again, gravitation prevails in our body precisely as it does elsewhere. Why should the blood not fill the vessels of the lowest levels of the organism and the back, the nates, the calves, and the heels of the recumbent patient become hypostatically congested, red, and hot, while his toes, knees, abdomen, and face, blanched and cold, reveal by their pallor and coldness the total absence of blood, which has gone to find its level? Instead of this the *entire* surface is frigid and blanched; the lowest portions of the body as well as the uppermost show that all the peripheral capillaries are depleted and collapsed, the blood in them having been drawn internally: *i.e.*, toward the great abdominal trunks. Again, the intensity of the pain seems to indicate not mere engorgement, but inordinate, disruptive, centrifugal pressure, for which mere relaxation of the vascular walls cannot account.

On the whole, we are forced to conclude that there must be an overpowering display of centripetal flux from the peripheral capillaries, arterial and venous, as soon as the vaso-constrictor mechanism fails to hold the central vascular walls up to their normal tone. That it is mechanical is suggested by its mode; that it enters into the domain of hydrokinetics is evident; and that loss of the normal equipoise between two forces forms the basis of the process affirms itself on all sides. The solution of the problem suggests itself when we recall, besides the fact that the total sectional area of the capillaries is seven hundred times that of the aorta, the manner in which the capillaries are affected when muscular vessels are dilated. The blood in them, as we have seen, is compressed by the resiliency of their walls and other tissue surrounding them, and literally floods the abdominal organs. Indeed, *the peripheral system contains as many sources of pressure as there are capillary tubes in it*—enough many times to account for all the mooted points just reviewed.

To illustrate the violence of the power exerted in this con-

nection, I may refer to the principle of hydrokinetics,—Pascal's principle,—which underlies the whole mechanical process. This physicist completely filled a strong cask with water, closed it hermetically, then inserted the end of a long, narrow, and close-fitting glass tube through a hole in one of the staves. Into the upper end of the tube, which stood upright, he then slowly poured water. Long before the tube had been filled the cask burst, owing to the excessive pressure within its walls. How was this pressure exercised? "The pressure of a fluid being due to its weight," the pressure in the upper layers of the water in the tube was slight, while that in its lower layers had increased in proportion with its distance from the top, since "pressure at any point in a liquid varies as its depth." "A pressure exerted on a fluid inclosed in a receptacle" being "transmitted undiminished to every part of that receptacle, and the total pressure exerted on the interior of the latter" being "equal to the area multiplied by the pressure per unit of area," a centrifugal display of force occurred—which far surpassed the resistance of the cask, and it had to yield. The hydraulic press, by means of which the hand of a child can break a steel rail, is based upon this principle.

These principles prevail in the human organism precisely as they do elsewhere in Nature. In the large vascular trunks of the abdomen, abdominal and thoracic viscera, etc., we have closed channels typifying the cask; in the narrow muscular vessels leading to them we have a multitude of conduits portraying the glass tube. Finally, we have the aggregate of pressure of millions of contractile, resilient capillary vessels containing a mass of blood (so great in comparison to the larger vascular structures that these have been considered as subsidiaries to the capillary system) to represent the gobletful of water with which Pascal indirectly caused explosion of his cask. That we have ample power to account for the symptoms mentioned is evident. It also accounts for suprarenal hæmorrhage when violent toxæmia is present. The rich vascular supply of the organs is well shown in the annexed colored plate prepared by J. M. Flint in the course of an exhaustive study of their anatomy, and published in the Johns Hopkins Hospital Reports.

Obviously the application of this principle is subject to limitations which the volume of blood accumulated in the vessels of the trunk impose. Admitting, for purposes of illustration, that all the blood of the organism has been forced into the interior of the body, its mass represents a fixed area which the various internal structures must furnish. Thus, while the large vascular trunks bear the brunt of the pressure, all the neighboring organs, including their capillaries, become engorged in proportion as the quantity of blood added to their normal contents is great. In other words, the blood accommodates itself to any room it can find after the larger vascular trunks are engorged, whether it be in a blood-vessel or a viscus. Thus, Boinet, in 45 of his 59 decapsulated rats, found hæmorrhage in the lungs in 16, in the spleen in 41, in the thyroid in 13, in the thymus in 11, in the kidneys in 8, in the liver in 5, and in the spinal cord in 5.

All this further emphasizes the practical bearing of the postulate: "Vessels supplied with a muscular coat and capillaries are antagonistic in contraction and dilation." It illustrates, furthermore, the importance of remembering that those toxins and other poisons which cause accumulation of blood in the splanchnic area also cause passive congestion of the *adrenal vessels* owing to the proximity of these channels and their direct relations with this area. This would occur for example with curarine, of which Tillie⁶⁶ writes: "With larger doses *there is dilation of the abdominal vessels* and hence accumulation of blood, little or nothing of this fluid entering the empty ventricle, notwithstanding that the heart may continue to beat.

When, therefore, we are dealing with infections such as Asiatic cholera, true cholera infantum, the anæmias, and other disorders in which extreme pallor prevails; or in acute intoxication by arsenic, chloral, alcohol, ptomaines, the coal-tar autopyretics and other agents which also provoke cutaneous pallor, there is good ground for the belief that, in addition to the recession of blood to the deep channels of the splanchnic area, and into the viscera, *including the adrenals*, we should take into account Pascal's hydrokinetic principle. Indeed, we are not dealing here with a single stream, as in the experiment referred

⁶⁶ Tillie: Medical Chronicle, March, 1891.

to, but with a multitude of streams derived from all the peripheral capillaries of the body. Moreover, we have, as an additional factor tending further to project the blood inwardly, the resiliency of the peripheral arterioles when the blood-stream passing through them is insufficient to cause them to retain their normal relative caliber.

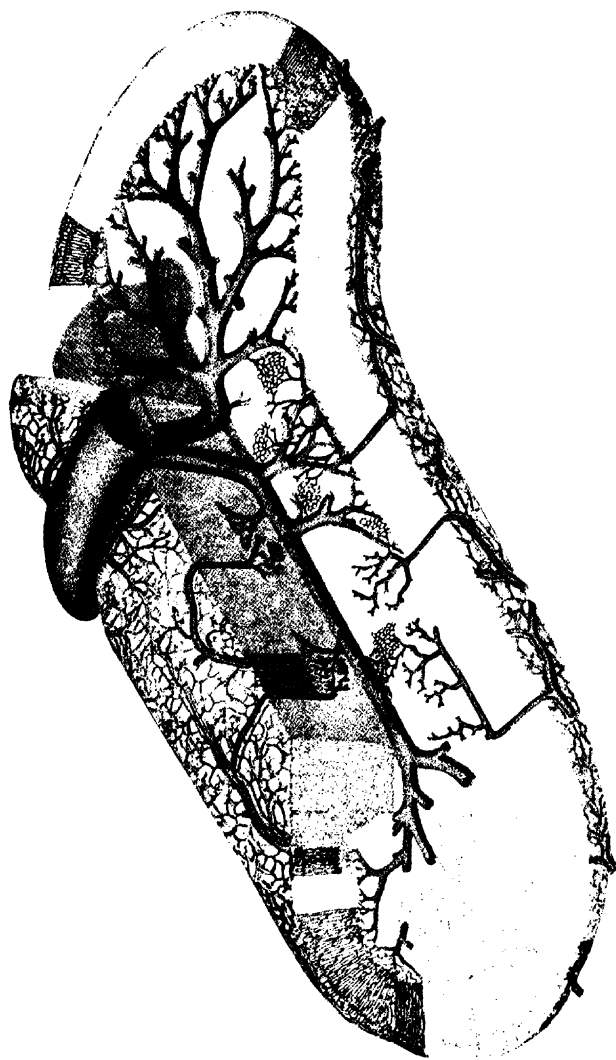
All these mechanical factors added to the passive hyperæmia incident upon the accumulation of blood in the splanchnic area seem clearly to expose the adrenals to a degree of centrifugal pressure at least equal to that produced by marked elevation of the general blood-pressure. It seems permissible to conclude, therefore, (1) *that the adrenals may become passively congested by the accumulation of blood in the splanchnic area and the abdominal viscera, caused by toxins and other poisons and drugs which markedly lower the blood-pressure, and* (2) *that the disruptive power of this adrenal congestion is enhanced by the centripetal pressure of the peripheral blood (Pascal's principle) and also by the pressure due to the resiliency of the peripheral blood-vessels.*

The heart, lungs and brain being correspondingly despoiled of blood, their functions are inhibited in proportion.

DEGENERATIVE EFFECTS OF TOXINS AND OTHER POISONS ON THE ADRENALS.—This is another factor which must be taken into account, especially where toxins are concerned. They show a wide range of selective power, and, in keeping with all sufficiently active poisons, are capable of irritating tissue cells and of causing necrosis and degeneration.

Before studying the manner in which the adrenals react under the influence of these poisons, it may be well to illustrate the primary steps of the process in accord with previously submitted conclusions, viz., the hyperæmia and the absence of pathogenic organisms in the glands proper. René Wybauw, for example,⁷⁰ injected diphtheria toxin into the peritoneal cavity of a large number of guinea-pigs, causing death within three days. In all these animals the adrenals had become somewhat enlarged and showed intense hyperæmia, the central vein being particularly engorged. In one of the animals the disease fol-

⁷⁰ René Wybauw: *Annales de la Société Royale des Sciences Méd. et Nat. de Bruxelles*, vol. vi, p. 134, Nos. 2 and 3, 1897.



CIRCULATION OF THE ADRENALS IN THE DOG. [J. M. Flint.]

[*Johus Hopkins Hospital Reports.*]

lowed an acute course; the vascular structures had yielded to the pressure and the organs showed abundant hæmorrhages. The reticular and medullary zones, in which capillaries are especially abundant, presented the most marked lesions.

We have already seen that Abelous and Langlois also found that the injection of various bacterial cultures caused vascular lesions varying from slight congestion to severe hæmorrhage. Two cases, also referred to previously, are particularly interesting in this connection: In the one, a case of acute toxæmia reported by Andrewes,⁷¹ death occurred in 36 hours, and the adrenals alone showed lesions—interstitial hæmorrhage. In the other, reported by W. S. Colman,⁷² the symptoms also indicated a general infection; death occurred in about 25 hours, and no lesion other than suprarenal interstitial hæmorrhage was found. The interesting feature of these cases, however, is that both observers submitted blood taken from the hæmorrhagic foci in the organs to bacteriological examination. Andrewes invariably obtained sterile cultures, and he states that, if any organisms were present, "there were none that grew upon ordinary media or stained with ordinary reagents." Colman not only reached the same result with blood from the adrenals proper, but with blood taken from other organs. The cases had doubtless been caused by a specific toxin, but with the ever-present hyperæmia as the only morbid feature.

But this is evidently but a stage of the morbid process, succeeded by local lesions. Wybauw⁷³ states that he has invariably found in these organs, after the injection of diphtheric toxins in rabbits, the histological lesions found elsewhere in this disease.

He further noted that the point of union of the reticular and medullary zones, where the capillaries are especially numerous, presented the well-known type of degeneration, while the slides also clearly showed all the stages of cellular destruction, with more or less disintegration of the nuclei. The latter were also undergoing retrogressive stages, gradual loss of regular outline, irregular perimetric retraction, etc. He likewise

⁷¹ Andrewes: *Lancet*, May 7, 1898.

⁷² W. S. Colman: *Lancet*, May 7, 1898.

⁷³ Wybauw: *Loc. cit.*, pp. 134 and 166.

examined microscopically the adrenals of a guinea-pig killed with cholera germs, but in this connection he says: "The adrenals are the seat of much less pronounced changes than those of the diphtheric guinea-pig. They are redder than normal. But the examination shows lesions which must certainly be produced by the same mechanism. The cells are irregular, the nucleus having lost in places its characteristic structure," etc. In a case of broncho-pneumonia following tracheotomy for diphtheria, he was able to note the same changes that he had observed in the diphtheric rabbits and choleraic guinea-pigs, but less marked, the patient having died of the concomitant disease before the diphtheric process had become far advanced.

Arnaud,⁷⁴ in a case of suprarenal hæmorrhage associated with liver-abscess, also found lesions in the suprarenal medulla characterized by cellular degeneration, granular disintegration, etc.: *i.e.*, a general necrobiosis of septic origin. If to these results we add those of Andrews and Colman, referred to above, it would seem permissible to conclude with Wybauw, that bacterial toxins possess a direct irritative action upon adrenal tissue.

But this observer ascribes to the adrenals a special sensitiveness to the influence of diphtheric toxins. While this may be true, it is more likely that, inasmuch as a specific toxin does not produce a characteristic lesion in them, the phenomena witnessed, histological and symptomatic, should rather be considered as expressions of excessive stimulation or exhaustion of these organs common to all toxins. The various toxins differ in potency precisely as do other poisons; it is also self-evident that various poisons must affect the adrenals in proportion as their virulence and dose are great.

The common action of various toxins is suggested by other facts. Thus, Langlois and Charrin⁷⁵ invariably noted hypertrophy of the suprarenal tissues after the prolonged use of diphtheric toxins in small quantities, in guinea-pigs. In one of the animals the organs had increased to over four times their normal size. The same phenomena followed injections of *Bacillus pyocyaneus*. Petit⁷⁶ also found hypertrophy to fol-

⁷⁴ Arnaud: *Loc. cit.*, p. 15.

⁷⁵ Langlois and Charrin: *La Médecine Moderne*, Feb. 5, 1896.

⁷⁶ Petit: *Loc. cit.*

low filtered cultures of the Löffler bacillus in fishes. That the hypertrophic process is overactive is shown by the fact that hypertrophy also occurs in the remaining gland when one has been extirpated. Stilling⁷⁷ observed that in young rabbits the remaining adrenal sometimes attained very large size; Auld⁷⁸ also reported several instances in cats. In the presence of these facts it is evident that the adrenals are submitted to excessive activity when certain toxics appear in the blood-stream, and that the local lesions are the expression of a physiological function utilized beyond its normal limits. The histological lesions found post-mortem are no longer pathological manifestations; they are those of physiological overuse or overwork.

That we are dealing with the effects of overactivity is sustained by evidence from another direction. In the instances in which hypertrophy was caused by injections of toxins these were administered in small doses at frequent intervals, the process extending over a period of many weeks. If we analyze Wybauw's report, there are points which tend to indicate even more than the direct effects of toxins noted. This author refers to promiscuously distributed swollen cells, the protoplasm of which is less clear than usual, and to other features that recall the characteristics of cloudy swelling observed most frequently in the liver and kidney and in the heart-muscle. This we know may be caused not only by toxins, but also, and with equal frequency, by nutritional disturbances excited by nervous stimulation,—a fact which recalls that electrical stimulation of the splanchnic nerve increases the functional activity of the adrenals.

What these organs are exposed to under excessive stimulation, especially in the course of febrile infections and intoxications, is suggested in the following lines by Lazarus-Barlow;⁷⁹ "It is generally held that the cloudy swelling of pyrexial disease and the fatty changes of hyperthermia are to be associated, and many authors hold that cloudy swelling is a transitional stage in the pathological conversion of proteid into fat. It is certainly in favor of this view that cloudy swelling is most commonly

⁷⁷ Stilling: *Virchow's Archiv*, Dec., 1889.

⁷⁸ Auld: *British Medical Journal*, June 3, 1899.

⁷⁹ Lazarus-Barlow: "General and Exper. Pathology," p. 414, 1904.

seen in rapidly fatal and acute pyrexial disorders, fatty changes in chronic pyrexial disorders."

Again, we have seen the predominant rôle infections play in adrenal hæmorrhage. We shall now see to what extent the adrenals are the seat of fatty change, which means in this connection the frequency with which these organs are involved in disease:—

Arnaud,⁸⁰ alluding to the signs of fatty degeneration in the adrenals observed *post mortem*, writes: "This lesion, which is appreciable only by histological examination, is very common, as shown by my personal researches. It existed *to a more or less marked extent 36 times in 100 subjects* whose adrenals had been collected *at random* at autopsies." Rolleston⁸¹ refers to this subject in the following words: "In the suprarenal bodies of adults *fatty change is so common as to be a physiological condition*. The fat occurs as large globules in the cells. This change may be present throughout the whole of the cortex or be best marked in the zona fasciculata. The medulla is occasionally seen to be occupied by fat, but never to the same extent as the cortex, while in children there is little fat normally. Attlee found, however, some, though slight, fatty change in still-born children. In children dying from marasmus there was marked fatty change, which was more frequent than in the liver. The cortex was affected in all, and the medulla in 6 out of the 9."

Now, if we realize that it is only in febrile diseases and intoxications that cloudy swelling and fatty degeneration occur, and also that the proportion of deaths due to non-febrile processes is relatively large, it will become apparent that *the adrenals must be regarded as exposed to lesions endangering life in all diseases and intoxications attended by a high temperature*.

On the whole, a general summary of the evidence and the conclusions based thereon submitted in the foregoing pages seem to me to have demonstrated:—

1. *That the adrenals are greatly exposed, owing to their delicate structure and their location among the great blood-channels of the splanchnic area, to active and passive congestion of a dangerous type;*

⁸⁰ Arnaud: *Loc. cit.*, p. 6.

⁸¹ Rolleston: Allbutt's "Practice," p. 567.

2. *That in the course of any toxæmia the adrenals are liable (a) to cloudy swelling and fatty degeneration when the temperature and blood-pressure are high, and (b) to hæmorrhage when their internal vessels are unable to resist the centrifugal pressure of their blood;*

3. *That recovery from infections and toxæmias of all kinds depends to a material degree upon the extent of the lesions to which the adrenals are subjected during the active stage of the disease;*

4. *That high fever and high blood-pressure, on the one hand, and abnormally low temperature and low blood-pressure, on the other, are the signals that the adrenals are endangered.*

This suggests that drugs in large doses, unless used to counteract the morbid effects on the adrenals of the existing toxæmia, might react on these organs precisely as do toxins and other poisons. While experimental work upon this point is entirely inadequate to demonstrate that such is the case, there is considerable indirect evidence available to this effect.

MORBID EFFECTS OF DRUGS AND VENOMS ON THE ADRENALS.

—E. W. Adams,⁸² referring to a group of cases found in literature in which, after the use of adrenal extract in cases of Addison's disease—doubtless in excessive doses—he says, “Alarming results were presumably or possibly due to treatment.” One of the two instances of alarming collapse cited “began to improve markedly when the extract was stopped.” A surgeon, after grafting the adrenals of a dog into the abdominal cellular tissue of a girl fourteen years old, witnessed her death in three days. Another, having resorted to the same method in two cases, lost both within twenty-four hours, owing, he thinks, to the operation. The same result followed in a fourth case. Referring to three of these instances, the attending physician of the last case, P. Courmont, writes: “In the three the results were disastrous. In my own case the patient died in twenty-four hours with a formidable rise of temperature and cardiac collapse,” and without the least evidence of infection.

Why this “formidable rise of temperature”? Text-books of physiology make no reference to this symptom and it is not

⁸² Adams: *Practitioner*, October, 1903.

explained by the classic effects of adrenal extractives: a rise of blood-pressure, with slowing of the heart's action, and increase of its contractile power. And yet Reichert⁸³ and also Morel⁸⁴ have shown that adrenal extract caused a rise of as much as 1.8° F. (1° C.) in the rabbit, while Lépine⁸⁵ noted that this phenomenon was always a feature of the clinical use of adrenal preparations. In the first edition of the present work I had already explained (see next chapter) that the adrenal secretion sustained the oxidation processes of the entire organism.

It is apparent, therefore, that to the classic symptoms preceding death after removal of both adrenals: "great prostration, muscular weakness and marked diminution in vascular tone," as Howell⁸⁶ puts it in a recent edition of his text-book, we should add *diminution of the temperature*—an effect first pointed out by Brown-Séquard. The fact that the hypothermia is discernible both on the skin and in the rectum indicates that it is not due to recession of the blood from the surface to the splanchnic area, while hypothermia, sensation of cold, etc., are, as is well known, prominent symptoms of Addison's disease.

We have seen under the preceding heading how toxins and various poisons may impair or even annul the functions of the adrenals. Might not drugs in *full doses* do likewise? It seems as clear that the phenomena caused by *toxic doses* are to a certain extent due to the primary effects of these agents—meaning by "primary effects" those that occur early in the course of the process of intoxication—on the blood-pressure, whether by producing excessive vascular tension or the opposite condition, very low blood-pressure, both of which may cause engorgement (active or passive) of the adrenals.

Taking as landmarks the three salient symptoms that follow removal, or destructive disease, of the adrenals: muscular weakness, and lowering of the blood-pressure and temperature, we shall see below that they are ever-present signs of poisoning, *even though the physiological action of the drugs enumerated be totally different and essentially specific*. It is, of course, impossible to review the hundreds of drugs capable of proving

⁸³ Reichert: Univ. of Penn. Med. Bull., April, 1901.

⁸⁴ Morel: Le Progrès Médical, Aug. 3, 1903.

⁸⁵ Lépine: La Semaine Médicale, Feb. 18, 1903.

⁸⁶ Howell: Text-book of Physiology, 3d edit., p. 841, 1910. (The italics are mine. S.)

toxic in excessive doses; about thirty of the main ones will be reviewed, quoting from Wood's text-book (eleventh edition), those sentences which indicate the effects referred to, and in which inhibition of adrenal functions may, from my viewpoint, play a part.

MUSCULAR WEAKNESS.—Aconite is said by Wood to cause in therapeutic doses "a sense of muscular inertia and weakness," and if the dose administered be larger "the muscular weakness is extreme." Alcoholic muscular relaxation hardly needs to be insisted upon; the attitudes of drunkards speak for themselves. Antimony in large doses is referred to as causing great muscular relaxation, the exhaustion becoming extreme after toxic doses. Antipyrin acts according to the dose administered, causing rigidity in large doses (excessive momentary muscular tonus), while "in overwhelming amount," according to Blumenau,⁸⁷ it causes in frogs "muscular relaxation with loss of reflex activity deepening into complete paralysis and death." Arsenic causes, even in small doses in the frog, cessation of voluntary movement. The muscular weakness, lapsing into complete exhaustion, that follows arsenic poisoning, is a familiar clinical picture.

Belladonna—*i.e.*, its alkaloid, atropine—is referred to as follows: "When an enormous dose of the alkaloid has been taken, a fatal stupor, with muscular relaxation, may develop at once. . . . Probably, however, in all cases stupor and muscular paralysis finally develop." . . . Bromism, according to E. H. Clarke, is attended with "muscular weakness which becomes paralysis." Camphor is referred to as giving rise in large doses to a feeling of lassitude, while general paralysis follows the ingestion of poisonous doses. Carbolic acid is stated by Wood to give rise to muscular weakness, but a striking suggestion of a relationship between the effects of carbolic acid poisoning and disturbed suprarenal functions is the reference to the fact that in frogs and mammals "the paralyzing influences of carbolic acid are usually first manifested upon the hind-legs." . . . Chloral is referred to as producing muscular weakness and then paralysis. Labbé is stated to have found that after death the muscles respond perfectly to gal-

⁸⁷ Blumenau: St. Petersburger med. Wochenschrift, 1887.

vanism, thus eliminating organic alteration of the muscular tissues as a factor in the paralytic phenomena.

The muscular relaxation witnessed in chloroform anæsthesia needs only to be recalled. Cocaine is termed by Wood "a muscle-poison, stimulating and afterward depressing the functional activity." Copper is referred to as capable of causing progressive paralysis. Bókay⁸⁸ found that the muscles were affected very early by *continuous* doses, "cloudiness of their protoplasm and disappearance of their cross-striation coming on." This recalls the cloudy swelling previously referred to as observed even in the adrenals themselves, the precursor of fatty degeneration. Digitalis in toxic doses is said to cause lassitude, prostration, and muscular tremors. Ether anæsthesia, and the profound muscular relaxation produced, need only be mentioned. Hydrocyanic acid is termed a "paralyzant to the muscles," general paralysis ensuing almost immediately after taking a toxic dose. That the hind-extremities are first paralyzed in animals I have ascertained. The effects of mercury in this connection are well known,—*"mercurial palsy,"* which occurs within a few hours after the poison enters the organism; the *"peculiar brownish hue of the whole body"* . . . *"which generally accompanies the disease,"* also suggest adrenal insufficiency as an element of the process.

Opium was found as long ago as 1826 by Charvet⁸⁹ to cause "progressive loss of power in the contractile tissue, ending in death; in fishes, paralysis and convulsions; in birds and mammals, paralysis, convulsions, and stupor." In man "alarming depression" also occurs. Oxalic acid poisoning is stated to be attended with "entire prostration of strength." Phosphorus poisoning also produces "a sense of weakness and general wretchedness." Physostigma gives rise, after the full therapeutic dose, to "slight weakness and dislike for muscular exertion" and in large doses to "great muscular weakness." "When an animal receives a small fatal dose of Calabar bean, after a time muscular tremors appear, and almost immediately the victim falls to the ground or lies down in a state of perfect muscular flaccidity."

Strychnine in sufficiently large doses produces "muscular

⁸⁸ Bókay: *Pester med.-chir. Presse*, 33, 1897.

⁸⁹ Charvet: *Pereira's "Materia Medica,"* 1036, Philadelphia, 1854.

twitchings and startings and formications," while toxic doses induce spasm, opisthotonos, etc. The high blood-pressure caused by strychnine and convulsions is pre-eminently of the kind calculated to provoke adrenal lesions. Although as recently shown by Cannon, Aub and Binger^{89a} minute doses of nicotine stimulate the adrenals, tobacco poisoning is known to cause "absolute loss of muscular strength" and finally complete collapse. Veratrine is referred to as primarily a muscle-poison, a stage of hyperexcitability preceding the stage of paralysis. Zinc poisoning is attended with prostration. As to chronic poisoning by this metal, Wood refers to the experiments of Sacher,⁹⁰ who found that intravenous injections of very large doses of zinc salts produced paralysis of the voluntary muscles.

We thus have typified in all these various poisonous agents not only the typical muscular weakness observed in recognized diseases of the adrenals and the total prostration following removal of the organs, but we can also discern in the list grades of muscular function ranging from slight weakness to total paralysis. How, *along with other organs*, are the adrenals influenced? A clue to this may be obtained by a brief review of the effects of *venoms*, using for this purpose an excellent paper published by Noé,⁹¹ and more recent experimental labors.

Vulpian called attention, in 1869, to the progressive asthenia, followed by somnolence with motor phenomena recalling those of curare poisoning, caused by cobra-venom. Paul Bert noted also that muscular activity disappeared after scorpion toxæmia and that the muscles failed to respond to strong induction currents. Now, the labors of Delezenne,⁹² Flexner and Noguchi,⁹³ Noc⁹⁴ and others have shown that certain venoms, those of the cobra, rattlesnake and viper, caused (1) hæmolysis, thus depriving the blood of oxidizing power, and (2) proteolysis, thus exposing various tissues to digestive destruction and the walls of the blood-vessels to softening. This furnishes an explanation of the intense muscular weakness which follows these venoms, the muscles being no longer, owing to the deterioration

^{89a} Cannon, Aub and Binger: Jour. of Pharmacol. and Experimental Therap., March, 1912.

⁹⁰ Sacher: Thesis, Dorpat, 1893.

⁹¹ Noé: Arch. génér. de médecine, Jan., Feb., Sept., and Nov., 1899.

⁹² Delezenne: C.-r. de l'Acad. des Sciences, Aug. 11, 1902.

⁹³ Flexner and Noguchi: Univ. of Penna. Med. Bulletin, vol. xv, p. 345, 1902, and vol. xvi, p. 163, 1903.

⁹⁴ Noc: Annales de l'Institut Pasteur, June, 1904.

of their *pabulum vitæ*, the blood, to contract. Yet, are the adrenals not supplied with the same blood? Obviously, their functions must also be arrested and the *asthenia* which always follows their functional arrest *added* to that due to the effects of the blood on the muscles.

That a similar arrest of their functions should occur under the influence of drugs which are capable—just as toxins and other poisons were shown to be, under the last heading—to cause intense congestion, venous engorgement, hæmorrhage into the adrenals, seems self-evident. Indeed, Luksch⁹⁵ found that, both in uræmia and phosphorus poisoning, the blood-pressure curves corresponded in degree with the morbid changes in these organs. We may thus have *inhibitive congestion or hæmorrhage* caused by drugs which in large doses *raise the blood-pressure materially*; or again *passive congestion and stasis and hæmorrhage* in the case of drugs which *greatly lower the blood-pressure* in large doses. Indeed, we may have *inhibition of the adrenals through ischæmia* by drugs such as their own active principle which greatly constrict their arterioles, as will be shown in the second volume. The *asthenia* of adrenal origin can thus be caused by drugs which affect the blood-pressure seriously in any manner.

VARIATIONS OF THE BLOOD-PRESSURE.—Precisely as is the case with destructive disorders of the adrenals, so do venoms and toxic doses of drugs cause decrease of the blood-pressure.

Kauffmann is referred to by Noé as having observed that viper-venom at once causes enormous reduction of arterial pressure. "It is especially marked in the digestive tract," says this author, "a true gastro-intestinal apoplexy; it is the main cause of death." Phisalix, on the other hand, observed that viper-venom caused general vasodilation, congestion of all organs, rapid lowering of blood-pressure, and weak pulse; and found the blood to contain but a small amount of CO₂. Couty also observed vasodilation after injections of rattlesnake-poison.

The presence of *increased* vascular pressure capable of causing adrenal hæmorrhage is illustrated by the effects of smaller doses or weaker poisons. Thus, Phisalix and Langlois⁹⁶

⁹⁵ Luksch: *La Riforma Medica*, Apr. 29, 1905.

⁹⁶ Phisalix and Langlois: *Académie des Sciences*, Sept. 6, 1899.

are stated to have found that salamandrine in small doses stimulated cardiac action and greatly increased vascular pressure in dogs, while large doses gave rise to ecchymotic spots and hæmorrhages.

The same variations of pressure, cardiac and vascular, are observed in connection with drugs. Acetanilid in toxic doses, as is well known, may cause a peculiar cyanotic condition of the face and extremities, while "the fall of temperature is accompanied by profuse sweating." . . . "In rare cases," says Wood, "the lowering of the bodily temperature has been coincident with the occurrence of collapse." This is always attended by a marked decline of the blood-pressure. "In frogs," writes Wood, "the phenomena caused by aconite are similar to those seen in man, and consist of, at first, a reduction and, afterward, an increase in the rate of the heart's beat, with a loss of power in the circulation, and, finally, irregular systolic movements, with marked prolonged diastolic pauses ending in diastolic arrest." Alcohol is referred to as acting upon the heart as a stimulant in small doses and as causing increase of arterial pressure. A large dose, on the other hand, is followed by a fall of arterial pressure and acts as a muscle depressant. Antimony is another agent which, like acetanilid, seems rapidly to induce suprarenal insufficiency. "In the lower animals," writes Wood, "all doses of antimony sufficient to cause any apparent effect progressively lower the arterial pressure; the pulse is sometimes at first temporarily accelerated, but usually the slowing of the pulse occurs from the beginning of the poisoning. During this period of slow pulse the diastolic pauses are extremely long and the pulse-waves greatly augmented, it may be to five times their original size. After a time the pulse usually becomes very rapid, the pulse-waves very small, the arterial pressure almost extinguished, and in a few minutes diastolic arrest occurs." The process referred to in these remarks, based on the experiments of Ackermann⁹⁷ and Ernst Sentz,⁹⁸ underlies the clinical phenomena familiar to all as well as those of Asiatic cholera, cholera infantum, and cholera morbus.

Antipyrin resembles acetanilid in its action. "Demme,

⁹⁷ Ackermann: *Virchow's Archiv*, xxv, 531.

⁹⁸ Ernst Sentz: *Inaugural Dissertation*, Dorpat, 1853.

Arduin, Armand, H. Casimir,⁹⁹ and Cerna and Carter¹⁰⁰ have separately determined by experiment that in moderate doses antipyrin increases the arterial pressure, while toxic doses lower the pressure." "The toxic dose of arsenic," says H. C. Wood, Sr., "greatly lessens the rate and force of the pulse-beat and markedly lowers the blood-pressure." He refers to the experiments of Unterberger,¹⁰¹ who "found that in an animal under the influence of the poison neither galvanization of a sensory nerve nor of the vasomotor center in the upper cord had any influence upon the force of the blood-current." The reason for this is apparent with inhibition of the adrenals as a factor of the process. Belladonna, or, better, its alkaloid, atropine, it is stated, "may cause a primary slowing of the pulse (very brief and only to be occasionally demonstrated), followed by an extraordinarily rapid pulse, with a very great rise in the arterial pressure; followed, after a time, if the dose has been sufficient, by a progressive lowering of pressure until death is reached, the rapidity of the pulse being maintained until the end" . . . "in atropinized animals neither section nor galvanization of the vagi affects the pulse-rate."

Bromides, these apparently benign agents, stand in this connection as actively toxic as many of the more virulent drugs reviewed. They seem to inhibit suprarenal activity even in small doses. Schouten¹⁰² found that, during the injection of a 2-per-cent. solution into the vena cava of a rabbit, "the cardiac systole grew slower, the diastolic pauses longer, and finally the heart stood still." Wood considers it as "well established that large, toxic doses of the bromides exert a direct paralyzing action on the heart, lessening both the force and the frequency of the beat, and finally causing diastolic arrest." The relation between the arrest of adrenal secretory activity and cardiac arrest is apparent. Camphor is referred to as acting directly as a stimulant to the heart-muscle. Interesting, however, is the same author's reference to the contrary results reached by Alexander Lewin,¹⁰³ which he ascribes to "the use of overwhelming doses, camphor first stimulating and then depressing

⁹⁹ H. Casimir: Thèse de Lyon, 1886.

¹⁰⁰ Cerna and Carter: "New Remedies," 1892.

¹⁰¹ Unterberger: Archiv für exp. Path., etc., II.

¹⁰² Schouten: Archiv für Heilkunde, xii, 97, 1871.

¹⁰³ Alexander Lewin: Archiv für exp. Path., etc., 1890.

the heart-muscle." Carbolic acid he refers to in the following words: "The prominent symptoms induced by lethal doses are disturbance of respiration; stupor, deepening into coma; rapid, feeble pulse; muscular weakness; abolished reflexes; collapse; fall of temperature, and albuminous or bloody urine, etc." It is perhaps needless to point to these phenomena as the exact counterpart of total suprarenal insufficiency. Chloral at first causes slowing of the heart's action. "Very large doses," according to both Andrews and Da Costa,¹⁰⁴ "decidedly lessen arterial pressure. The characteristic influence of therapeutic, and still more of toxic, doses is to produce a fall in the blood-pressure, usually accompanied by a lessening in the frequency of the heart's action."

The preliminary stimulation of cardiac action induced by chloroform is well known. "Putting all the evidence together," writes Wood, "it seems to us to have been completely demonstrated by physiologists, first, that chloroform is a direct depressant and paralyzant to the heart-muscle or its contained ganglia; second, that the fall of blood-pressure which occurs in chloroformization is in great part due to this direct depression of the heart." Cocaine, as shown by various investigators, produces an increase of arterial pressure when given in moderate doses. "The drift of the present evidence," says Wood, "is to show that the small dose of cocaine moderately stimulates the heart, and that the large, toxic dose finally depresses it."

Copper is another agent the clinical phenomena of which recall those of cholera: toxic doses paralyze the heart in lower animals. Digitalis, in batrachians, raises blood-pressure and depresses it in the last stage. "In most of the experiments of J. P. Arnold and H. C. Wood, Jr., upon dogs," writes Wood, "the change from a slow to a rapid pulse has been abrupt and usually accompanied by an enormous rise of the already elevated blood-pressure. At the end, the fall of pressure is very sudden and rapid, so that it has immediately preceded death." . . . "It seems to be clearly established that in poisoning of the mammal by digitalis the heart is arrested, not in sys-

¹⁰⁴ Andrews and Da Costa: *American Journal of the Medical Sciences*, April, 1870.

tole, but in diastole." It also seems "very certain that the proposition framed for the lower mammals applies also to man." Now, section of the splanchnics, which contain the adrenal secretory nerves, arrests the action of digitalis.

Ether is referred to in the following terms: "Our present evidences show that there is, during ether anæsthesia, a rise of pressure, which is, at least in part, the result of cardiac action. . . . This rise is followed by a fall." Hydrocyanic acid depresses the vaso-motor and fall of the blood-pressure, according to Cushny; it was found by Preyer, Lecorché, and Meuriot to produce, in sufficient amount and concentration, instantaneous diastolic arrest. In large, though not enormous, doses Preyer and Laschkewitsch noted that "it first produced a sudden prolonged arrest of the heart, followed by an augmentation in the rapidity of the cardiac action, and after this a diminution of the rate: to the normal number in cases of recovery, to cardiac standstill in cases of death."

Mercury, in the form of corrosive sublimate, also gives rise to choleraic symptoms in toxic doses. "In the course of two or three hours," says Wood, "very rarely in less than an hour, collapse occurs, with small, frequent, irregular pulse." Opium is referred to as follows: "In man the circulatory phenomena are a slight primary evanescent acceleration of the pulse-rate (Nothnagel¹⁰⁵), succeeded by the characteristic slowing and increased fullness and force of the pulse, which is followed by a return to the normal pulse or a great increase of the rapidity and loss of strength during the third stage." Experimentally it was found to cause arrest of the heart in diastole. Dott and Stockmann found that large doses lowered the blood-pressure. Phosphorus, in the very acute cases of poisoning, may be attended with pronounced cardiac weakness, even in the primary stage. "The patient," says Wood, "may suddenly succumb to collapse and cardiac paralysis." Physostigma, injected in poisonous doses into the jugular vein, causes death from syncope or from simultaneous "failure of the cardiac and respiratory functions, and the heart is arrested in diastole. When smaller doses are exhibited, there is slowing of the heart's action." Santonin in toxic doses causes slowing of the pulse in dogs, and

¹⁰⁵ Nothnagel: "Handb. d. Arzneimittellehre," 1870.

rapid or slow, feeble pulse in children. Silver salts when injected into the veins were found by Charcot and Ball, Rabuteau and Mourier to cause instantaneous death, which is ascribed by these investigators to "a direct paralyzing influence of the drug upon the muscle of the heart." Strychnine is stated by Wood to produce in full dose "a rise of the arterial pressure, which is enormously increased during the convulsion, after which there is a very pronounced fall in the arterial pressure." Tobacco, or rather its alkaloid, nicotine, is referred to as having "a very distinct influence" upon the circulation, "producing, first, rise, and, afterward, fall, of pressure."

All the remarks concerning the influence of inhibition of the adrenals in the production of muscular weakness by toxic doses of drugs and venoms are applicable here. Venoms by dissolving the blood-elements *arrest adrenal functions*, and this contributes to the fall of blood-pressure. Or the latter may be caused by drugs (strychnine type) which *primarily raise the pressure* sufficiently to cause *inhibitive congestion or hæmorrhage of the adrenals*; or conversely by drugs which *primarily lower the pressure* sufficiently (arsenic type) and thus cause *inhibitive passive congestion and hæmorrhage* in these organs; or finally by drugs which, by causing excessive constriction of the arterioles (adrenalin type), *block the entrance of blood into the adrenals* and thus arrest their functions.

LOWERING OF THE TEMPERATURE.—The third typical sign of adrenal inhibition is quite as commonly observed as the two others reviewed. In one sense it is the most important of the three, for it represents, from my viewpoint, the symptom of which the arrest of adrenal functions stands as the direct cause, the adrenals sustaining, as will be shown in the next chapter, general oxidation.

Phisalix¹⁰⁶ refers to hypothermia as the main characteristic of viper intoxication. He found it to occur rapidly and to an intense degree, reaching in guinea-pigs as low as 22° C., though death usually occurred at 32° C. He also observed that hypothermia prevailed after injections of ichthyotoxin, or eel-venom, while Bottard¹⁰⁷ noted it in guinea-pigs after

¹⁰⁶ Phisalix: *Archives de Physiologie*, 1894.

¹⁰⁷ Bottard: *Thèse de Paris*, 1889.

injection of sea-dragon venom. Hutinel also observed it in a case of cobra-bite, the temperature of the patient, a man, reaching down to 31.2° C.

Acetanilid exemplifies the personal view that antipyretics do not really relieve hyperthermia, but in reality shift it to deeper organs. Wood refers to the experiments of Hare, subsequently confirmed by Evans, in which a distinct fall of temperature was observed to have followed the use of acetanilid in normal animals allowed to run free. In a criticism of these observations he writes: "In examining the records of the calorimetric experiments made by Hare and Evans on the normal animal, we find that not only did the *rectal temperature not fall* under the influence of antifebrin, but in nearly every instance there was a *distinct rise*, amounting in some cases to over a degree. It is evident, therefore, that these experiments cannot be used to explain how antifebrin reduces temperature when it does cause a fall." In truth, they *can* be used for this purpose, but only with *dilation* of the large vascular trunks of the abdomen, and secondary ischæmia of the peripheral capillaries as factors of the process. The internal congestion caused the rise of temperature observed by Wood; the peripheral depletion caused the lowered temperature observed by Hare and Evans. And so it appears to be with all drugs we term "antipyretics" whose main effects are exercised by withdrawing blood from the surface—shutting it off through the intermediation of a mechanism described in the second volume—and causing it to accumulate in the abdominal vascular trunks. This represents the type of drug in which passive congestion of the splanchnic area may involve the adrenals and cause inhibition of these organs.

The temperature in severe aconite poisoning is stated to undergo "a very pronounced fall," though at the very start it may rise slightly. Alcohol, a cardiac stimulant, at first raises the blood-pressure by becoming oxidized in the blood, but it was found by Ruge¹⁰⁸ to lower the temperature 3° C. when given in sufficient quantity to animals to produce narcosis, while a lethal dose reduced it 5° C. The flushed face of the drunkard betokens cutaneous hyperæmia with contraction of the abdominal vascular trunks and congested capillaries, while the pallor

¹⁰⁸ Ruge: Virchow's Archiv, xlix, 265.

of the advanced stage typifies the contrary condition. Antimony is also stated to perceptibly reduce animal heat. Wood refers to the observation of Ackermann, who observed a fall of 6.6° C. in rabbits that lived five hours. In fact, the term "cardiac depressant" means, in some instances, an adrenal depressant. Insufficiently supplied with its normal tone-giving element, the suprarenal secretion, the heart is arrested in diastole. Antipyrin likewise gives rise to a fall of bodily temperature, but we have here a set of symptoms which emphasize the presence of further advanced suprarenal insufficiency: an eruption followed by a brown pigmentation. Bullæ, which recall those previously referred to as observed in children whose adrenals were found hæmorrhagic *post-mortem*, also follow the use of this drug in some cases.

Arsenic poisoning has already been referred to as simulating cholera, for which, according to Wood, it has not only been mistaken "during life, but also on the post-mortem table." Here, the internal recession of blood, and the resulting adrenal congestion explain the effects of arsenic as well as those of cholera toxin, the phenomena witnessed including that of "icy coldness." Belladonna, with its alkaloid atropine, affords a good example of the antagonistic effects that always prevail. Stimulated to great activity by this drug, the central vascular trunks are contracted and the surface capillaries engorged at first. But, while the temperature may be raised by large doses, as is well known, poisonous doses will bring it down below normal. In animals this reduction has reached 5.1° C. The bromides in toxic doses, to use Wood's words, "lower very decidedly the temperature." We have typified in the effects of these agents continued insufficiency of the adrenals, just sufficient to keep up moderate peripheral capillary contraction, with resulting impaired nutrition: the so-called "bromism." Dougall's case,¹⁰⁰ in which $1\frac{1}{2}$ ounces of potassium bromide were taken in 24 hours, probably exemplifies total suprarenal insufficiency, weak pulse, cold extremities, temperature of 96.8° F., general cutaneous anæsthesia, coma, etc. Camphor, classed as an antispasmodic, is referred to as giving rise to "cool, pale, and livid skin" in poisonous doses. Carbolic acid, classed

¹⁰⁰ Dougall: Glasgow Medical Journal, Feb. 1893.

as antipyretic, was found by Hare¹¹⁰ to produce a very distinct fall of temperature in rabbits. Chloral, a somnifacient, is referred to by Wood as follows: "A most remarkable action of chloral is upon the temperature." In this particular all observers agree with Richardson, of London, who has seen the temperature fall 6° F. in a rabbit which recovered. Hammersten observed a fall of 6° C. (Wood) in an hour in animals well wrapped up and laid in a warm place.

Chloroform causes depression of the cardio-vascular system almost from the start. The central trunks, at first contracted, produce engorgement of the peripheral capillaries, causing facial congestion and suffusion, accompanied by cerebral excitement. When the dangerous stage comes on, the contrary occurs: dilation of the central trunks depletes the peripheral capillaries. The heart-muscle, more or less rapidly deprived of the adrenal secretion, fails, probably because, as shown by Oliver and Schäfer, it sustains the tone of cardio-vascular muscles. These phenomena coincide with the temperature changes. Simonin¹¹¹ "found that the temperature rises during the first stage (1.1° to 0.9° C.), falls slightly during the second or remains above normal, and falls decidedly during the third stage." Cocaine, a "delirifacient," is stated to cause a "rise of *rectal* temperature in cocaine poisoning, which sometimes amounts to as much as 8° F." . . . "It is certainly not due to convulsions," says Wood, "as it usually occurs before the motor disturbance." Copper sulphate was found by Falck¹¹² to cause great depression of temperature. Digitalis also lowers the temperature several degrees in healthy men and animals, this hypothermia being preceded by a temporary rise.

Ether was found by Angelesco¹¹³ to lower the temperature to a greater extent than chloroform. Hare states that "prolonged etherization lowers the bodily heat very greatly," and that, while a dog's temperature may be lowered 9° F., a fall of 4° F. has been noted in man. Hydrocyanic acid acts with such promptness that the distinction between hypothermia and the increasing coldness of the extremities preceding death cannot

¹¹⁰ Hare: *Therapeutic Gazette*, No. 519, 1887.

¹¹¹ Simonin: *Centralblatt für Chirurgie*, 234, 1877.

¹¹² Falck: *Deutsche Klinik*, vol. xi, 1859.

¹¹³ Angelesco: *La Semaine Médicale*, Dec. 14, 1894.

be differentiated. Mercury was found by Kuperwasser¹¹⁴ to lower the temperature 2° C., in some instances, when administered in injudicious doses. Opium and its alkaloids are referred to as causing the skin to become cold and moist when given in toxic doses. Oxalic acid in poisonous doses also gives rise to livid surface and cold skin. Phosphorus is often attended, when ingested in toxic doses, with what Wood terms "a remarkable fall in the temperature," the lowest point recorded some hours before death being 31.2° C. (88.2° F.). Physostigma brought the temperature of a strong man down to 96.6° F. Santonin poisoning is also attended with great coldness of the surface. Silver salts have likewise been found to lower the temperature of animals.

Strychnine is another agent which tends also to show the correctness of the contention that a low peripheral temperature means an increased central temperature. Wood refers to the observations of Kionka, who showed that "the primary elevation of temperature which occurs in strychnine poisoning, both in man and the lower animals, is in animals followed by a pronounced fall, which takes place even if the convulsions persist," and to the affirmations of Mosso,¹¹⁵ that "even in curarized dogs a very pronounced rise of *rectal* temperature may be produced by strychnine." Very suggestive in this connection is the denial credited to Delezenne,¹¹⁶ "who states that in curarized animals the exhibition of strychnine is always followed by an abatement of the central temperature, which is often, but not always, followed by an increase of the temperature of the surface." This increase Delezenne explains by "the supposition that the drug has the power of dilating the peripheral vessels." It now becomes evident that the only discrepancy between the observations of Mosso and Delezenne is that the latter used smaller doses of strychnine than the former, thus producing central contraction and peripheral dilation, instead of central dilation and peripheral contraction. Tobacco, veratrum, and zinc show corresponding effects, and close the list of agents whose temperature variations are considered

¹¹⁴ Kuperwasser: Archives des Sciences Biologiques de St. Pétersbourg, No. 6, 1898.

¹¹⁵ Mosso: Archives italiennes de Biologie, 1886.

¹¹⁶ Delezenne: Bulletin Médical du Nord, xxxiv, 1895.

along with other toxic effects. All present a reduction of peripheral temperature as a sign of advanced poisoning; none show simultaneous central and peripheral hypothermia; several incidentally show that, when peripheral hypothermia is present, there is simultaneous internal hyperthermia.

The personal view that the adrenal secretion becomes converted in the lungs into the oxidizing principle of the hæmoglobin (see next chapter), and thus sustains oxidation in all tissues, accounts for the morbid effects of poisonous doses of drugs and venoms on the temperature. *Congestion of the adrenals*, active or passive, is caused by *drugs capable, in full doses, of raising or depressing the blood-pressure*. If this congestion or engorgement is excessive, or sufficient to cause adrenal hæmorrhage, *it may inhibit or arrest the functions of the adrenals, and thus cause hypothermia*.

Venoms, which lower the temperature mainly by dissolving the blood-cells, thus inhibiting the oxygenizing power of the blood, *also inhibit the functions of the adrenals* by this process; but they likewise do so by *causing excessive variations of the blood-pressure* as do other poisons, thus affording *an additional cause of hypothermia*.

SUMMARY OF THE MORBID EFFECTS OF DRUGS AND VENOMS ON THE ADRENALS.—In the light of the conclusions submitted in the foregoing sections (pages 34 to 54) concerning the manner in which the functions of the adrenals are compromised by variations of the general blood-pressure, on the one hand, and the morbid influence on the blood-pressure and through it on the adrenals of *toxic doses* of drugs, on the other, I submit the following conclusions as important in the clinical field:—

1. Drugs, such as antipyrin, alcohol, belladonna, cocaine, digitalis, ether, mercury, opium, strychnine, quinine, etc., whose action in full doses is to *raise* the blood-pressure, cause marked asthenia, hypotonia and hypothermia *in toxic doses*, because they produce, among other effects: *acute congestion and perhaps hæmorrhage of the adrenals, and thus inhibit or arrest the functions of these organs*.

2. Drugs, such as aconite, arsenic, antimony, chloral, hydrocyanic acid, physostigma, tobacco, veratrine, etc., whose action in full doses is to *lower* the blood-pressure, cause marked

asthenia, hypotonia and hypothermia in *toxic doses*, because they produce, among other effects: *passive congestion or venous stasis and perhaps hæmorrhage of the adrenals, and thus inhibit or arrest the functions of these organs.*

The symptoms produced by arrest of adrenal functions are the same in both groups of drugs, viz., weakness, lowering of the blood-pressure and temperature; but these same symptoms are also the most prominent ones in Addison's disease and after removal of both adrenals.

We have seen on page 38 that all this applies equally well to *toxins*—a subject treated at length in the next chapter.

3. *Venoms.*—The labors of Delezenne, Flexner and Noguchi, Noc and others having shown that some venoms—cobra, viper, rattlesnake, and others—caused (1) hæmolysis, thus depriving the blood of its oxidizing power, and (2) proteolysis, thus exposing various tissues to necrobiosis and the vessels to softening; *the adrenals receive blood incapable of sustaining their functions though destructive to their vascular and secretory elements; their secretory activity being impaired or arrested, the asthenia, hypotonia and hypothermia from this source intensify the same symptoms due to the effects of this disorganized blood upon other tissues.*

Destined to suggest new lines of thought, the present work would have to be restricted to this chapter, in so far as the adrenals are concerned, were the prevailing views as to their functions—that they serve to sustain the tone of the cardiac and vascular muscles—taken as sole guide. But, as is now well known, I have held for several years that this rôle is but an incidental feature of their true functions—an assertion I hope fully to sustain in the next chapter.

CHAPTER II.

THE FUNCTIONS AND DISEASES OF THE ADRENALS.

UNEXPLAINED PROPERTIES OF THE ADRENAL SECRETION.

As we have seen, adrenal preparations—extracts, the powdered gland, the active principles, epinephrin, supracapsulin, adrenalin, etc.—cause a rise of the blood-pressure with slowing of the heart-beat, a minute dose sufficing to produce a marked effect. But, as Howell¹ states, “the effects produced by such extracts are quite temporary in character. In the course of a few minutes the blood-pressure returns to normal, as also the heart-beat, showing that the substance has been destroyed in some way in the body, although *where and how this destruction occurs is not known.*” All that is established is that, as stated by Swale Vincent,² the secretion is formed in the adrenal medulla, and that “it passes by way of the adrenal veins into the general circulation, in order to assist the activity, or maintain the tone of sympathetically innervated muscle and other tissue,” the latter including, as shown by Cardone,^{2a} the skeletal muscles. The fate of the secretion in the blood has not been determined. From my viewpoint, *it forms part of the respiratory mechanism, as a constituent of the hemoglobin, besides acting as stated above.*

Adrenal preparations are all endowed, as first observed by Vulpian many years ago, with marked reducing activity, *i.e.*, with a marked tendency to take up oxygen. Abel, who isolated the adrenal active principle he termed “epinephrin,” for instance, found this tendency so marked that it proved a source of inconvenience. Takamine noted that the colorless aqueous solution of his “adrenalin” was easily oxidized by contact with the air, its color changing from pink to red, and eventually to brown. Cybelski also observed that the addition of potassium permanganate, a powerful oxidizing agent, destroyed the activity of

¹ Howell: *Loc. cit.*, p. 842.

² Swale Vincent: “Internal Secretions and the Ductless Glands,” London, 1913.

^{2a} Cardone: *Il Policlinico*, fasc. 11, 12, 1910.

adrenal extract. What is the relationship between this reducing property and the blood-pressure raising power?

Various experimenters and clinicians, including Reichert,³ Morel,⁴ and Lépine,⁵ have observed that even non-toxic doses of adrenal preparations caused a rise of temperature. Others, Courmont,⁶ for example, found that adrenal grafts could produce such a rise as to warrant the phrase "formidable hyperthermia." Conversely we know that destructive disorders of the adrenals, Addison's disease, for example, or removal of the adrenals, cause a rapid decline of the temperature. This suggests that the adrenal secretion must be endowed with oxidizing power, and yet we have seen that it is a reducing agent. How account for this anomaly and for the power of adrenal products to raise the temperature?

When the adrenal tissue is excessive, as in the hypernephroma of children, there is excessive oxidation and overnutrition of the subject. The process of growth and development are such in some cases as to cause a child to appear several times its age—a child of 4 years, for example, being as large as one of 16. How account for this phenomenon as a result of an excessive production of adrenal secretion, which presumably occurs when the secreting elements are also in excess?

Not all vessels are influenced by the adrenal secretion or extractives. A striking fact in this connection is the apparent exemption of the pulmonary tissues to the effects of the secretion. Wallace and Mogk⁷ found that, while adrenal extract caused a rise of the systemic blood-pressure due to the contraction of *the arterioles*, the pressure in the pulmonary arteries is not raised, these vessels, in their opinion, not being acted upon as are the others. This observation was confirmed by Brodie and Dixon.⁸ Velich,⁹ on the other hand, found, by a series of experiments instituted to ascertain whether vasoconstrictor fibers existed for the pulmonary vessels, that adrenal extract gave rise to but a slight rise of pressure. Warm adrenal extract, which,

³ Reichert: Univ. of Penna. Med. Bull., April, 1901.

⁴ Morel: Le Progrès Médical, Aug. 3, 1903.

⁵ Lépine: La Semaine médicale, Feb. 13, 1903.

⁶ Courmont: Congrès de Médecine Interne, Montpellier, 1898.

⁷ Wallace and Mogk: Transactions of the Physiological Society, Dec. 28-30, 1898.

⁸ Brodie and Dixon: Journal of Physiol., vol. xxx, p. 416, 1903.

⁹ Velich: Wiener med. Wochenschrift, No. 26, 1898.

when applied even to the skin, causes pallor, was found by him to exercise no such effect upon the surface of the lungs. This accounts for the familiar fact upon which Parhon and Golstein¹⁰ lay stress, that intravenous injections of adrenalin can produce acute pulmonary œdema, owing doubtless to the marked rise of blood-pressure in the rest of the organism. Why this exception?

Such were the questions which I attempted to answer in the first edition of this work, which appeared in 1903. The only experiments on the connection between the adrenal secretion and respiration had been those of Oliver and Schäfer and Langley—the injection of adrenal extracts into animals, with temporary arrest of respiratory movements—due doubtless to spasm of the respiratory muscles—as result. But obviously they taught nothing as to the respiratory process *per se*. When, however, the avidity of the adrenal product for oxygen, its influence over general oxidation and nutrition, and the invulnerability of the lungs to its action, on the one hand, and the fact that both pulmonary and tissue respiration still belonged to the domain of conjecture, on the other, are taken into account, there was good ground for the belief that a connection between the adrenals and the respiratory process actually existed.

THE ADRENAL SECRETION AS THE OXIDIZING AGENT OF THE HÆMOGLOBIN.

That the prevailing view on the physiology of respiration, based on the diffusion of gases, has not been, and is not now, endorsed by all physiologists is now well known. “When,” writes Professor Mathias Duval,¹¹ of Paris, “an animal is caused to breathe in the smallest possible space—the air imprisoned in its lungs—it uses up all the oxygen in the air. This is because hæmoglobin, in virtue of its chemical affinity, *takes up the oxygen as fast as this gas is dissolved in the serum*,¹² so that the latter, always despoiled, is never able to satisfy its absorption coefficient for oxygen, however low be this coefficient, and however slight be the tension of the oxygen in the surrounding air. As to the exhalation of carbonic acid, it is not produced so simply as would *a priori* seem, by mere gaseous diffusion or by

¹⁰ Parhon and Golstein: *Loc. cit.*, p. 725.

¹¹ Mathias Duval: *Cours de physiologie*, 1892.

¹² All italics are my own.

the mere giving off of a gas in solution, because of the scarcity of the gas in the surrounding atmosphere. Indeed, the air in the pulmonary vesicles contains 8 per cent. of carbonic acid, hardly a favorable condition for the escape of carbonic acid from the blood, especially since a portion of this gas is not dissolved, but combined with the serum salts. It is therefore probable that the pulmonary tissues are the seat of an action having for its object to rapidly dislodge the carbonic acid. *This action is probably of a chemical nature.* . . . Whenever oxygen is mixed with venous blood, even *in vitro* during experiments, the carbonic acid is immediately given off. One is led to admit, therefore, that the combination of oxygen with the blood-corpuscles (oxyhæmoglobulin) plays a rôle analogous to that of an acid, and involving the elimination of carbonic acid from venous blood." He refers to Robin and Verdeil's view in respect to the existence of a hypothetic "pneumonic acid" and to the experiments of Garnier,¹³ who observed that ultramarine blue, sprayed into the lungs of living guinea-pigs, lost its color: a phenomenon which could only occur through the presence of a strong acid, neither taurin nor carbonic acid being capable of producing it. "Chemical analysis of the lung has not disclosed a specific acid, however."

"It is, perhaps, wrong," adds Professor Duval, himself a prominent physiologist, "for physiologists to continue to only see in these phenomena mere results of endosmosis of liquids and of diffusion of gases through an inert membrane." As a clinician, I would urge that this theory is harmful in its far-reaching consequences. I have pointed out that the *acrotonometer*, upon which it is mainly founded, is a defective instrument, and that it is because of this that the results recorded by various physiologists have been divergent to such a degree that, in some instances, the diffusion of oxygen should occur, to correspond with its indication in the wrong direction, *i.e.*, from the hæmoglobin to the alveolar air, the tension of oxygen in the arterial blood being actually higher than the pressure of oxygen in the air-cells.

I characterize the prevailing theory as "harmful" because the physiologist, engrossed in his own field, does not realize that

¹³ Garnier: *Comptes-Rendus de l'Académie des Sciences*, July 26, 1886.

he is dealing with the foundation of probably the most important problem of our day in its influence over human life, viz., immunity not only in the tissues at large, but at the very threshold of infection—the pulmonary alveolar surface, and the alimentary canal, as will be shown later.

THE ADRENAL SECRETION IN PULMONARY RESPIRATION.—In the first edition of the present work (1903) I advanced the view, sustained by considerable evidence, that the adrenals took a leading part in the respiratory process by supplying a secretion which absorbed the oxygen of the air in the pulmonary alveoli, then became a part of the hæmoglobin and of the blood-plasma, which in turn carried it, as oxidizing principle, to all tissues.

Three years after this opinion was formulated, a noted English physiologist, Pembrey, wrote¹⁴ in an impartial review of the recent advances in physiology and bio-chemistry: "It is impossible to give a satisfactory account of the gaseous exchange between the blood and the alveolar air." . . . "The body of evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen." This theory is that of Bohr, advanced in 1891, which attributes the oxygen-absorbing power and the excretion of carbon dioxide to active secretory processes carried on by the lining membrane of the air-cells. While the need of a secretion capable of absorbing the oxygen has been steadily growing in favor, however, the secreting membrane has not been found.

This is explained when the respiratory process is considered from my viewpoint: *It is not by a local membrane that the reducing secretion is produced, but by the adrenals.* As shown below, its properties and itinerary are precisely those required for the process, while its presence can be traced at every step to the hæmoglobin itself, of which it forms part.

A succinct review of the experimental evidence which has invalidated the diffusion doctrine, and of that upon which my conception of the respiratory process is based, will perhaps serve better than a prolonged analysis of the question (for which the reader is referred to previous editions) to convey the actual status of the question.

¹⁴ Pembrey: Hill's "Recent Advances in Physiology and Bio-Chemistry," p. 549, 1906.

Paul Bert,¹⁵ thirty years ago, showed experimentally that the absorption of oxygen by the pulmonary blood persisted, even when the pressure of this gas was almost *nil*. Müller also observed that a strangulated animal exhausted the air in its lungs of *all* its oxygen, while Setschenow and Holmgren,¹⁶ Zuntz,¹⁷ and others found but traces of oxygen in the arterial blood of asphyxiated animals. This suggested that the diffusion doctrine was defective, and that the absorption of oxygen from the air was due to the presence, in the blood circulating through the lungs, of some substance capable of taking up this gas. This conclusion was sustained by the researches of Bohr,¹⁸ Haldane and Lorrain Smith,¹⁹ Vaughan Harley,²⁰ and Bohr and Henriques,²¹ the last-named investigators referring to it as a substance "having greater avidity for oxygen than the blood itself" and presumably "a kind of internal secretion."

This view has been antagonized by some of the advocates of the diffusion theory (whose aërotonometric figures are suggestively discordant), but as we have seen the "evidence has been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen."

Having repeatedly noted the powerful reducing properties of adrenal extractives, it occurred to me that the secretion of the adrenals might fulfill this rôle. Anatomical studies in various lower animals and in man, and a systematic research in the literature of the subject, demonstrated that it met all the conditions required to satisfy so important a function.

The first deduction imposed by these researches was that

The secretion of the adrenals has a marked affinity for oxygen, and inevitably reaches the pulmonary air-cells.

Vulpian,²² over fifty years ago, found that adrenal juice reduced iron perchloride and iodine. Cybulski²³ recorded a similar action on potassium permanganate; Langlois²⁴ noted, however, that adrenal extract lost its reducing properties *in vitro*

¹⁵ Paul Bert: C. r. de l'Acad. des sci., Oct. 28, 1873.

¹⁶ Setschenow and Holmgren, cited by Ludwig: Wiener med. Jahrb., 21st year, 1, p. 145, 1865.

¹⁷ Zuntz: Hermann's "Handbuch," iv, part 2, p. 43, 1882.

¹⁸ Bohr: Skandin. Archiv für Physiologie, p. 236, 1891.

¹⁹ Haldane and Lorrain Smith: Jour. of Physiol., xxii, No. 3, p. 231, 1897.

²⁰ Vaughan Harley: *Ibid.*, xxv, No. 1, p. 33, 1899.

²¹ Bohr and Henriques: Arch. de physiol., ix, pp. 459 and 819, 1897.

²² Vulpian: C. r. de l'Acad. des sci., p. 663, Sept. 29, 1856.

²³ Cybulski: Gazeta Lekarska, 2d series, xv, pp. 299-308, 1895.

²⁴ Langlois: Arch. de physiol. norm. et pathol., x, p. 124, 1898.

when oxidizing compounds were added. As to the action of the atmospheric oxygen, Battelli²⁵ found that adrenalin did not lose its properties when contact with air was prevented, while Abel,²⁶ Takamine,²⁷ and others refer to this property as a source of trouble in laboratories, the latter chemist specifying, in fact, that adrenalin becomes oxidized by contact *with the air*.

That the adrenal secretion inevitably reaches the air-cells was made clear by a study of the anatomical relations between the adrenals and the lungs. The blood of the efferent vessels of the adrenals, their veins, passes to the inferior vena cava, directly on the right side, and by way of the renal vein on the left. The actual presence of the adrenal secretion in the blood of the adrenal veins is shown by many experimental facts. Gottschau,²⁸ for example, traced hyaline granules (found subsequently to be their secretion) from the interior of the adrenals to their veins. This observation was confirmed and amplified by Manasse,²⁹ Aulde,³⁰ and Stilling.³¹ Pfaundler³² traced the same granules from the interior of the organ along the adrenal veins to the vena cava itself. It is doubtless the adrenal secretion and no other which is carried by the blood of the vena cava, for, when blood originating from the adrenals on its way to this great trunk was injected into animals by Cybulski and Seymonowicz,³³ it produced the characteristic effects of adrenal extract. These results were confirmed by Biedl,³⁴ Langlois,³⁵ and Dreyer.³⁶ Seymonowicz, Biedl, Dreyer, Salvioli, and Pizzolini³⁷ found, moreover, that such effects could not be obtained with venous blood obtained from other parts of the body.

The next fact to assert itself was that

On reaching the air-cells, the adrenal secretion absorbs oxygen and becomes a constituent of hæmoglobin and of the red corpuscles.

²⁵ Battelli: C. r. de la Soc. de biol., liv, p. 1435, 1902.

²⁶ Abel: Bull. Johns Hopkins Hosp., p. 215, Sept.-Oct., 1898.

²⁷ Takamine: Therapeutic Gazette, p. 221, April 15, 1901.

²⁸ Gottschau: Arch. f. Anat. u. Physiol., Anat. Abth., p. 412, 1883.

²⁹ Manasse: Arch. f. Path. u. Physiol., cxxxv, p. 263, 1894.

³⁰ Aulde: Brit. Med. Jour., May 4, 1894.

³¹ Stilling: Arch. f. path. Anat., cix, p. 324, 1897.

³² Pfaundler: Sitzungsber. d. k. Akad. d. Wissensch. Mathem., cl, p. 3, 1892.

³³ Cybulski and Seymonowicz: Gazeta Lekarska, 2d series, xv, pp. 299-308, 1895; Archiv f. d. ges. Physiol., lxi, Nos. 3 and 4, p. 97, 1896.

³⁴ Biedl: Archiv f. d. ges. Physiol., lxvii, part 9-10, 1897.

³⁵ Langlois: Arch. de physiol. norm. et pathol., ix, p. 152, 1897.

³⁶ Dreyer: American Journal of Physiology, ii, p. 203, 1899.

³⁷ Salvioli and Pizzolini: Gazzetta degli osped., Mar. 23, 1902.

While a reducing substance has been found necessary, we have seen, to account for the absorption of oxygen from the alveolar air, it happened that the greater part of the hæmoglobin molecule was composed almost entirely of an albuminous substance which had remained unidentified. Gamgee,³⁸ for instance, states that "hæmoglobin exists in the blood-corpuscles in the form of a compound with a yet unknown constituent of the corpuscles." This body he defines as the "albuminous moiety of the hæmoglobin molecule" and,³⁹ as representing 96 per cent. of this molecule, the remaining 4 per cent. being the iron-laden hæmatin. Now, I found that this "unknown constituent" of hæmoglobin corresponded in its physicochemical properties with the adrenal secretion. Gamgee,⁴⁰ for example, states that hæmoglobin is insoluble in absolute alcohol, chloroform, benzol, ether, and all organic solvents: Vulpien⁴¹ had already noted that, of all glandular products, that of the adrenals alone showed this peculiarity. Gautier,⁴² Moore,⁴³ and Takamine also refer to it. Again, according to Moore and Purinton,⁴⁴ adrenal extracts are rapidly destroyed by alkalis; this is also a characteristic of hæmoglobin. This pigment likewise resists heat up to the boiling point; this applies also, according to Cybulski,⁴⁵ Moore,⁴⁶ and others to adrenal extract. Finally, Mulon⁴⁷ found that the red corpuscles gave the histochemical reactions of the active principle of the adrenals, thus showing that these blood-cells actually contain this principle. Since then the adrenal reaction has been obtained from blood-elements wherever sought, including that of the placenta.

In confirmation of this conclusion is the fact that

The oxygen-laden adrenal secretion is a constituent of the albuminous hæmoglobin in the blood-plasma.

Battelli⁴⁸ and Kraus^{48a} found adrenalin in the blood, the latter author in Graves's disease. That this principle is a constituent of the albuminous portion of hæmoglobin voided

³⁸ Gamgee: Schäfer's "Text-book of Physiology," i, p. 189, 1898.

³⁹ Gamgee: *Ibid.*, p. 207, 1898.

⁴⁰ Gamgee: *Ibid.*, p. 206, 1898.

⁴¹ Vulpien: C.-r. de l'Acad. des Sci. de Paris, Sept. 29, 1856.

⁴² Gautier: Chimie biologique, p. 355, 1892.

⁴³ Moore: Journal of Physiology, xvii, p. xiv, 1894-95.

⁴⁴ Moore and Purinton: American Journal of Physiology, lii, p. 15, 1900.

⁴⁵ Cybulski: Gazeta Lekarska, Mar. 23, 1895.

⁴⁶ Moore: *Loc. cit.*

⁴⁷ Mulon: Personal Communication.

⁴⁸ Battelli: C.-r. de la Soc. de Biol., liv, p. 1179, 1902.

^{48a} Kraus: Cited by Brugsch, Folia Therapeutica, Jan., 1909.

by red corpuscles in the plasma suggested itself when Schmiedeberg,⁴⁹ Jaquet,⁵⁰ Abelous and Biarnès,⁵¹ and other chemists showed that blood-plasma contains an oxidizing substance, subsequently known as oxidase. Not only was it found to resist heat at least up to the boiling point and to possess other chemical characteristics of the adrenal principle, but the actual presence of the latter is confirmed by other facts. Thus, in 1853, Traube had concluded that hæmoglobin could not fulfill the physicochemical functions ascribed to it without the aid of a catalyzer. Poehl⁵² showed that the adrenal principle was a catalyzer, while Jolles⁵³ pointed out that the activity of a given volume of blood as a catalyzer corresponded with the number of red corpuscles it contained. It is because of this that Oliver and Schäfer found that oxidation of the adrenal principle does not occur in the blood; acting as a catalyzer it simply transfers oxygen from the pulmonary air to the tissues without being itself modified by the contact. Finally, Bernstein and Falta⁵⁴ recently found that "injections of adrenalin in healthy persons produced an increase of the consumption of oxygen and of the production of carbonic acid together with an increase of the respiratory quotient."

Additional evidence to this effect and an explanation of the rôle of the red corpuscles were afforded by the next conclusion reached: That

The red corpuscles, after absorbing the oxygenized adrenal secretion (the albuminous constituent of their hæmoglobin) yield it to the blood-plasma in the form of droplets, the so-called "blood-platelets."

As Gamgee⁵⁵ teaches, hæmoglobin, under the influence of various chemical agents, "undergoes a decomposition of which the chief products are, an *albuminous* substance or substances, and a *coloring matter* which contains the whole of the iron"; but, as he also says, "the coloring matter of the red corpuscles is not extracted from them by the plasma." This does not, however, apply to their albuminous substance. That they discharge the

⁴⁹ Schmiedeberg: *Archiv f. exper. Path. u. Pharm.*, vi, p. 233, 1876.

⁵⁰ Jaquet, cited by Salkowski: *Archiv f. path. Anat.*, Jan. 4, 1897.

⁵¹ Abelous and Biarnès: *Arch. de physiol. norm. et pathol.*, 5th series, vii, pp. 195, 239, 1895.

⁵² Poehl: *Indian Lancet*, May 22, 1904.

⁵³ Jolles: *Münch. med. Woch.*, p. 2083, Nov. 22, 1904.

⁵⁴ Bernstein and Falta: *Abst. in London Lancet*, June 29, 1912.

⁵⁵ Gamgee: *Loc. cit.*, i, p. 189, 1898.

latter in the plasma is rendered evident by various facts. Louis Elsberg,⁵⁶ thirty years ago, observed "a projection of a pediculated granule or knob" from the periphery of red corpuscles. Hirschfeld⁵⁷ traced these granules from the interior of these cells, through one or more minute apertures which closed up again, to the surrounding plasma. Brockbank⁵⁸ gave recently a beautiful microphotograph of "platelets in, or being extruded from, red cells." Again, Detemmann⁵⁹ noted that the buds on the surface of the red cells "at first are attached to the cell by protoplasmic processes and contain hæmoglobin"; but that, "later, the buds become separated from the cell, losing their hæmoglobin." This does not militate against Gamgee's statement that the coloring matter remains in the corpuscles, but it indicates that the albuminous constituent is voided into the plasma.

These albuminous droplets (which, in 1903,⁶⁰ I identified as the familiar *blood-platelets*), having absorbed oxygen in the lungs, should, in the light of preceding deductions and owing to the catalyzing property of their adrenal principle, be able to surrender their oxygen to any agent in the blood or tissues possessed of sufficient reducing power to appropriate it. That this applies to the droplets is shown by the reaction to certain stains. Litten⁶¹ and others found, for example, that blood-platelets derived from the red corpuscles are best stained with methylene-blue; Stengel, White, and Pepper⁶² state, in fact, that "methylene-blue gave the only positive results." This indicates that the droplets are certainly rich in oxygen—as their identity as the oxygenized adrenal secretion would suggest—for, as Ehrlich teaches, one of the conditions "essential to the methylene-blue reaction" is "oxygen saturation."⁶³

A study of the melanins then showed that

The albuminous constituent of the hæmoglobin, or oxygen-laden adrenal secretion, is distributed by the red corpuscles to all parts of the body as an oxidizing agent.

⁵⁶ Louis Elsberg: *Annals of the N. Y. Acad. of Sci.*, 1, 1879.

⁵⁷ Hirschfeld: *Virchow's Archiv*, clxvi, part 2, p. 195, 1901.

⁵⁸ Brockbank: *Med. Chronicle*, Mar., 1908.

⁵⁹ Detemmann: *Deut. Archiv f. klin. Med.*, lxi, part 4, p. 365, 1898.

⁶⁰ Sajous: *The present work*, 1st ed., vol. 1, p. 715, 1903.

⁶¹ Litten: *Deut. med. Woch.*, No. 44, Nov. 2, 1899.

⁶² Stengel, White, and Pepper: *Amer. Jour. Med. Sci.*, May 9, 1902.

⁶³ Quoted by L. F. Barker: *New York Medical Journal*, May 15 *et seq.*, 1897 to 1898.

Leonard Hill,⁶⁴ Hirschfeld, Chittenden and Albro,⁶⁵ and most classic writers look upon melanins, the brown and black pigments found in certain forms of sarcoma, in the tissues, the blood, the urine, etc., in various morbid states, as hæmoglobin derivatives. While Mörner, Brandl, and L. Pfeiffer⁶⁶ found that it contained iron, and accept this origin, Nencki and Berdez⁶⁷ do not, because they failed to find this metal in the pigment isolated from a melanotic sarcoma. These discordant opinions are harmonized, however, by the newer conception I submit: The first-named authors dealt with whole hæmoglobin, containing, therefore, its iron; while Nencki and Berdez dealt quite as surely with hæmoglobin, but only with its albuminous constituent.

Having traced to the adrenals the origin of the active agent of this albuminous hæmoglobin and this substance being melanin, the presence of the adrenal principle in melanins should be shown. In the first place these pigments were found by Walter Jones⁶⁸ insoluble in alcohol, ether, benzol, chloroform, etc., *i.e.*, precisely as Vulpian, Moore, and others had found to be the case with the adrenal principle. This applies as well to the action of alkalies, to which Jones, Abel and Davis⁶⁹ found melanins very sensitive, and to other tests. In the second place direct evidence was afforded by Boinet,⁷⁰ who found chemically that the bronze pigment of Addison's disease was identical to melanin, and also by Mühlmann,⁷¹ who discovered independently that the Addisonian pigment was a product of the adrenals.

Finally, as the connection of the adrenal product with respiration and oxygenation I urge, suggests:—

An excess of adrenal secretion causes a rise of temperature.

This action was first observed by Oliver and Schäfer.⁷² Reichert⁷³ recorded a rise of 1° C. in the dog, having reached this temperature "in less than forty minutes." In three experimental animals it "continued hypernormal for over two hours."

⁶⁴ Leonard Hill: "Text-book of Chemistry," p. 374, 1903.

⁶⁵ Chittenden and Albro: Amer. Jour. of Physiol., ii, p. 291, 1899.

⁶⁶ Mörner, Brandl, and L. Pfeiffer, cited by Hammarsten: "Text-book of Physiological Chemistry," 5th American Ed., p. 688, 1908.

⁶⁷ Nencki and Berdez: *Ibid.*

⁶⁸ Walter Jones: Amer. Jour. of Physiol., ii, p. 380, 1899.

⁶⁹ Abel and Davis: Jour. of Exper. Med., i, p. 381, 1879.

⁷⁰ Boinet: Marseille méd., April 15, 1896.

⁷¹ Mühlmann: Deut. med. Woch., No. 26, p. 409, 1896.

⁷² Oliver and Schäfer: Jour. of Physiol., xviii, p. 230, 1895.

⁷³ Reichert: Univ. of Penna. Med. Bull., April, 1901.

Morel⁷⁴ noted a rise of 0.5° to 1° C. (0.9° to 1.8° F.) in guinea-pigs. Lépine⁷⁵ states that the increase of blood-pressure caused by adrenal extract is always followed by a rise of temperature. This is controlled by the familiar fact, first observed by Brown-Séquard, that removal of the adrenals is followed by a steady decline of temperature and by the hypothermia which attends Addison's disease.

Additional evidence on this particular feature of the general problem will be found in Volume II. I studied, for example, the evolution of the red corpuscles throughout the animal scale⁷⁶ and learned that they were tardy additions to the blood as storage cells when the hæmoglobin diffused in the plasma, as it is in many invertebrates and in certain low vertebrates, failed to satisfy the needs of the vital process. Having been brought to the conclusion that, contrary to what is now taught, it is the plasmatic hæmoglobin which carries oxygen to the tissues and not the red cells (though these act as storage cells for it as a constituent of their albuminous hæmoglobin), I traced this substance in various tissues and organs, including the nervous system, the guaiac and methylene-blue tests being those most frequently employed. Again, I found that the oxidases gave the reactions of the oxygen-laden adrenal secretion. Hence the term I applied to the latter: *adrenoxidase*.⁷⁷

On the whole; this evidence, considered collectively, seems to me to afford a solid foundation for the conclusion that

It is the adrenal secretion which, after absorbing oxygen from the pulmonary air and being taken up by the red corpuscles, supplies the whole organism, including the blood, with its oxygen. It is, as such, the oxidizing constituent of the hæmoglobin, which, in turn, sustains tissue oxidation and metabolism.

This latter function is treated in detail in the second volume. "That the suprarenals are related *in some way* to metabolic changes in the tissues and organs," says Schäfer,⁷⁸ "there can be but little doubt. This is indicated by the symptoms of Addison's disease."

Additional evidence in favor of this conception of the rôle

⁷⁴ Morel: *Le Progrès médical*, Aug. 3, 1903.

⁷⁵ Lépine: *La Semaine médicale*, Feb. 18, 1903.

⁷⁶ Sajous: *The present work*, p. 828.

⁷⁷ Sajous: *Ibid.*, p. 822.

⁷⁸ Schäfer: *British Med. Jour.*, June 6, 1908.

of the adrenal secretion is afforded by the fact that it accounts, as will be shown by a few examples, for the properties of the adrenal secretion and preparations that the prevailing restricted view fails to explain.

Increased oxidation clearly accounts, for instance, for the observations of Reichert, Morel, Lépine and others, referred to above, that even non-toxic doses of adrenal extractives produce a rise of temperature, or those of Israel⁷⁹ which showed the great frequency of fever in tumors of the adrenals, or those of Courmont⁸⁰ in which adrenal grafts produced without the least evidence of infection what he characterized as a "formidable hyperthermia." In the latter cases it persisted until death occurred. Nor is it an ephemeral phenomenon, as is the case with the rise of blood-pressure, in the experimental use of adrenal preparations, for, as Reichert observed in his experiments, the high temperature persisted as much as two hours in some of the animals.

Again, adrenal preparations are familiarly known to raise the blood-pressure; but, obviously this tells us only *what* they do, but not *how* they do it. This becomes clear, however, when the adrenal secretion as the active constituent of hemoglobin is regarded as the oxidizing agent of the tissues, and, as such, an active factor in metabolism. The muscular elements of the arteries being themselves the seat of increased metabolic activity, they are caused to contract, thus raising the blood-pressure. As shown by Oliver and Schäfer, however, there is also a direct action on the arterioles, and by Meltzer⁸¹ a similar action on the endothelium of the capillaries. This local effect is due also to the enhanced metabolic activity of the adrenal product, its identity as catalyzer enabling it to activate oxidation in any tissue with which it comes into contact.

The excessive growth of children caused by hypernephroma also finds its normal explanation in the inordinate oxidation, due to the overproduction of adrenal secretion. F. de Mira^{81a} found experimentally that the adrenals stimulated growth in general. The surplus of metabolic activity clearly accounts for the enhanced nutrition.

⁷⁹ Israel, cited by Moffitt: *Boston Med. and Surg. Jour.*, Oct. 8, 1908.

⁸⁰ Courmont: *Congrès de Médecine Interne*, Montpellier, 1898.

⁸¹ Meltzer: *Amer. Jour. Med. Sci.*, Jan., 1905.

^{81a} F. de Mira: *C-r. de la Société de Biologie*, Oct. 25, 1912.

In its relations to general diseases, the identity of the adrenals as the controlling agents of oxidation accounts for that ubiquitous symptom, *fever*, the mechanism of which has also remained obscure. This gives these organs a prominent place in pathology. Indeed, if the modern doctrine that fever up to a certain limit is the outward expression of an auto-protective or immunizing process is sound—and the bulk of evidence strongly sustains this view—the adrenals, as direct factors in fever, become also direct factors in protecting the body against disease. Their rôle in the economy thus assumes noble proportions in the extreme, since by their influence on tissue oxidation *the adrenals* sustain life, while through their participation in immunity they defend life.

Addison's disease may be due, as is well known, to tuberculosis, cancer, cirrhosis, and other organic disorders of the adrenals, or to pathologic changes in the solar plexus and semi-lunar ganglia. But *how* do these lesions cause the Addisonian syndrome in all its complexity? Many theories have been vouchsafed, but, in truth, as Anders⁸² puts it, "the pathologic connection between the symptomatic phenomena of Addison's disease and the anatomic lesions has not been made out." Now, consider the disease with the adrenal's as governing oxidation and metabolism: The adrenals being the seat of destructive lesions, these three conjoined functions increasingly show signs of deterioration; hence the low temperature and clamminess due to deficient oxidation; the marked and progressive asthenia, with great lassitude, due to inadequate metabolism in all muscles; the small and feeble pulse and weak heart action and steady lowering of the blood-pressure due also to inadequate metabolism in the cardiac and vascular muscles; the tendency to vertigo and the mental torpor due to ischemia of the cerebrum, the result, in turn, of the general vasodilation and of the resulting withdrawal of blood into the deep vessels, and, finally, the bronzing, due likewise to vaso-relaxation and circulatory torpor, the latter entailing the deposition in the epidermis of what has been found chemically to be the oxidized adrenal product, *i.e.*, melanin.

The experimental production of glycosuria by injections of adrenalin reported by Blum, Croftan, Herter, and others is now

⁸² Anders: "Practice of Medicine," p. 489, 9th ed., 1909.

familiar to every one. The labors of Pollak⁸³ have shown that, as I had previously suggested, this form of glycosuria was due to some relationship between the adrenal product and the hepatic glycogen. But what is this relationship? Here, again, the rôle of the adrenals in oxidation and metabolism supplies the explanation: By raising the blood's asset in oxygen, the adrenal active principle injected raises the rate of metabolic activity throughout the entire organism, including, of course, the pancreas. This organ being caused to secrete an excess of amyllopsin, which in turn converts an excess of glycogen into sugar, the proportion of the latter in the blood soon exceeds the needs of the body, and the surplus is eliminated in the urine. The participation of the adrenals themselves in the process is controlled by various facts. Herter, for example, found that glycosuria was caused when the adrenals were compressed in such a way as to increase the outflow of secretion, while, conversely, ligation of the adrenal veins which transfer the secretion to the inferior vena cava caused the sugar to diminish rapidly, both in the blood and in the urine. That our resources in the treatment of diabetes are enhanced by due consideration of the part played by the adrenals in one of its forms is soon shown by therapeutic results obtained.

Many other disorders the pathogenesis of which is obscured and the treatment of which is unsatisfactory, mainly owing to the fact that the adrenals are overlooked in their pathogenesis, are described in detail in the second volume. The facts submitted in the foregoing pages will suffice, however, to suggest that *the function now attributed to the adrenals, i.e., that of sustaining the tone of the vascular system, is but an epiphenomenon of its true function: that of sustaining pulmonary and tissue respiration.*

THE GOVERNING CENTER OF THE ADRENALS.

THE PITUITARO-ADRENAL NERVE.

That organs fulfilling such important duties in the organism as the above should be governed by some nerve-center almost imposes itself when we consider that many functions of relatively minor importance—color vision, coughing, sweating, ear

⁸³ Pollak: Arch. f. exper. Path. u. Pharm., Bd. lxi, S. 149.

movements, etc.—are supplied with one. My researches in this connection first showed that:—

The governing center of the adrenals is neither located in the cerebrum nor in the medulla oblongata, but in some organ at the base of the brain.

Removal of both hemispheres does not influence temperature, as shown by Frédéricq,⁸⁴ Goltz, and others. Corin and van Beneden⁸⁵ found in fact that, in decerebrated pigeons, the oxygen intake and the carbonic acid output did not differ from that of normal pigeons. Pembrey⁸⁶ states moreover that “the rapid rise in temperature which occurs when a hibernating marmot awakens is not prevented by removal of the cerebral hemispheres.” This applies as well to so high a mammal as the dog, in which, as shown by Goltz,⁸⁷ removal of the hemispheres, including a part of the optic thalami and corpora striata (whose functions are also annulled by removal of the cortex, the impulses of which they transform and transmit), did not interfere with any purely vegetative function. Evidently, therefore, although the hemispheres and the basal ganglia can, when the seat of lesions, cause a rise of temperature, the heat center is not located in these organs.

The base of the brain, however, asserts itself as a pathway for thermogenic impulses. While Tschetschichin, in 1866, Schreiber,⁸⁸ and Reichert⁸⁹ located a thermoaugmentor center in the pontobulbar region, Ott,⁹⁰ Tangl,⁹¹ and Sakowitsch⁹² obtained a marked rise of temperature by producing lesions higher up, *i.e.*, in the floor of the third ventricle and the tuber cinereum. But, as Richet has long held, and as Schäfer⁹³ states, examination of such experiments shows that “the results are closely dependent upon the establishment of an irritative lesion in parts which are either directly in or in close proximity to the path taken by motor impulses.” On the whole, the thermogenic lesions in the basal tissues must have irritated nerve-paths from some structure beneath the hemispheres.

⁸⁴ Frédéricq: *Arch. de biol.*, III, p. 747, 1882.

⁸⁵ Corin and van Beneden: *Ibid.*, VII, p. 265, 1889.

⁸⁶ Pembrey: Schäfer's “Text-book of Physiology,” I, p. 864, 1898.

⁸⁷ Goltz: *Arch. f. d. ges. Physiol.*, II, p. 570, 1892.

⁸⁸ Schreiber: *Ibid.*, VIII, p. 576.

⁸⁹ Reichert: *Jour. Amer. Med. Assoc.*, January 18, 1902.

⁹⁰ Ott: *Therap. Gaz.*, June 15, 1903.

⁹¹ Tangl, cited by Ott: *Ibid.*

⁹² Sakowitsch: *Neurol. Centralbl.*, XVI, p. 520, 1897.

⁹³ Schäfer: *Loc. cit.*, II, p. 717.

Further study of the question then showed that:—

The pituitary body sends nerve-fibers upward to the tuber cinereum and the walls of the third ventricle, and thence to the pontobulbar region and spinal cord.

As just shown, the heat center can only be located beneath the brain and basal ganglia. Now, anterior to the optic thalami, the corpora striata, and the seat of the thermogenic lesions produced by Ott and others, there exists no organ capable of generating nerve impulses by way of the tuber cinereum other than the pituitary body. The labors of many investigators in recent years have overthrown the view that any part of the pituitary body of man is vestigial. As Herring⁹⁴ concluded recently on histological grounds, "it is an organ of physiological importance." The various kinds of nerve-cells, neuroglia-cells, and ependyma-cells described by Berkley in the posterior lobe are of as great physiological importance, from my viewpoint, as any in the body at large. Cushing⁹⁵ recently confirmed by a large number of experiments the fact previously emphasized by many investigators, that complete removal of the pituitary invariably produced death.

Sappey, Luschka, Müller, and others of the older anatomists refer to the presence of nerve-fibers passing from the pituitary body along its pedicle, up to the third ventricle. But it was only after the Golgi method had been introduced that this fact could be placed on a solid basis. Ramon y Cajal⁹⁶ then found that the fibers passed upward to a large nucleus behind the optic thalami. Joris⁹⁷ also found histologically that "numerous fibers descend in parallel lines along the pedicle of the pituitary. They do not all come from the retro-optic nucleus," he writes; "some come from regions *posterior* to the infundibulum". . . . Bearing directly upon the production of thermogenic impulses is the discovery by Gentès⁹⁸ of fibers which pass from the pituitary to the tuber cinereum. Andriezen⁹⁹ had also traced, in the white mouse, fibers from the pituitary to the pons.

We thus have a direct nerve path from the pituitary to the

⁹⁴ Herring: Quarterly Jour. of Exp. Physiol., 1, No. 2, 1908.

⁹⁵ Cushing: Jour. Amer. Med. Assoc., p. 249, 1909.

⁹⁶ Ramon y Cajal: Anales de la Soc. española de hist. nat., 2a Seria, xxiii, p. 214, 1894.

⁹⁷ Joris: Mém. Couron. de l'Acad. Roy de Belgique, xix, part 10, 1908.

⁹⁸ Gentès: C. r. de la Soc. de biol., iv, p. 1560, 1903.

⁹⁹ Andriezen: British Medical Journal, January 13, 1894.

pontobulbar region—the identical tract along which, at various points, the lesions produced by Ott, Tangl, Sakowitsch, and Reichert provoked a marked rise of temperature. We will see presently that this path is continued down the cord, and that it eventually reaches the adrenals.

The next feature determined was a striking functional correlation between the pituitary and the adrenals. Schäfer and Herring¹⁰⁰ recently emphasized this parallelism not only as to their function, but also as to their development and structure. I ascertained, for example, that

The pituitary, like the adrenals, influenced general oxidation and the temperature, and also general metabolism and nutrition.

Although removal of the hemispheres does not influence the temperature, as we have seen, removal of the pituitary deeply affects this process. Marinesco¹⁰¹ and Vassale and Sacchi¹⁰² observed that it was followed by increasing hypothermia. This cannot be ascribed to operative shock, for Masay¹⁰³ first trephined the sella turcica to expose the pituitary, and allowed the animal to recover after this—the most violent step of the experiment. The result of subsequent removal was the same. Andriezen¹⁰⁴ and other authors also refer to a steady decline of temperature. Paulesco¹⁰⁵ noted that this decline was progressive until death occurred. Pirrone¹⁰⁶ states that the main symptoms are referable to the “vascular and respiratory systems and the temperature.” The relationship with the respiratory process is further shown by the marked disturbances of this class, dyspnoea, polypnoea, etc., noted by Cyon, Andriezen, Masay, and other experimenters.

The impairment of general metabolism through deficient oxygenation must necessarily inhibit nutrition. Practically all investigators refer to rapid emaciation and cachexia as prominent symptoms. In a dog which survived sixteen days’ removal of the organ, Thaon¹⁰⁷ observed “a progressive emaciation, followed

¹⁰⁰ Schäfer and Herring: Philos. Transactions, excix, p. 29, 1906.

¹⁰¹ Marinesco: Bull. de la Soc. de biol., p. 509, June 4, 1892.

¹⁰² Vassale and Sacchi: Arch. Ital. de biol., xxii, p. 123, 1895.

¹⁰³ Masay: Arch. de la Soc. roy. de sci. méd. et nat. de Bruxelles, xii, part 3, p. 1, 1903.

¹⁰⁴ Andriezen: Loc. cit.

¹⁰⁵ Paulesco: Jour. de physiol. et de path. gén., No. 3, p. 441, 1907.

¹⁰⁶ Pirrone: Riforma medica, February 25, 1903.

¹⁰⁷ Thaon: L'Hypophyse, p. 90, 1907.

by death in extreme cachexia." Caselli,¹⁰⁸ Pirrone,¹⁰⁹ and Masay¹¹⁰ also allude to this phenomenon. Fuchs¹¹¹ and many other authors urge the close—though obscure—relationship between the pituitary and bodily metabolism. Striking evidence of the influence of the pituitary on metabolism and nutrition is afforded by its rôle in gigantism and acromegaly, the excessive growth during the period of hyperplasia of the organ, and the steady decline from the time degeneration of its anterior lobe begins. A relationship with the adrenals is suggested, moreover, by a familiar symptom of the cachectic stage of acromegaly, of which Harlow Brooks¹¹² says: "A general brownish pigmentation is present in the average case, which at times strongly resembles that found in Addison's disease."

Another feature attesting to the parallelism between the pituitary and the adrenals is that

The pituitary, like the adrenals, influences the blood-pressure.

Cyon¹¹³ and subsequently Masay¹¹⁴ found that excitation of the exposed pituitary caused a marked rise of blood-pressure—from 81 to 200 mm. Hg. in one instance. Masay attributed this action to the presence in the organ of a secretion which the excitation and accompanying pressure forced into the circulation. While no one can assert today that such a secretion is not produced by the pituitary body, the actual existence of such a secretion or its functions has not so far been demonstrated. The substance considered as such is rich in albuminous hæmoglobin, and it is the adrenal principle it contains which, in my opinion, causes the rise of blood-pressure obtained by injections of the extract. When the pressure is marked, the kidneys, being passively congested, dilate, and diuresis is caused. The effects observed experimentally are thus accounted for without the need of a secretion to do so. This applies also, from my viewpoint, to several so-called "internal secretions." Testicular juice or orchitic extract, for instance, is an oxidizing ferment and cata-

¹⁰⁸ Caselli: Studi anat. e sperim. sulla fisio-pat. della glandula pituitaria, 1900.

¹⁰⁹ Pirrone: *Loc. cit.*

¹¹⁰ Masay: *Loc. cit.*

¹¹¹ Fuchs: Wiener med. Woch., February 8, 1903.

¹¹² Harlow Brooks: Archives of Neurol. and Psychol., 1, p. 435, 1898.

¹¹³ Cyon: Arch. de physiol., x, p. 618, 1898.

¹¹⁴ Masay: *Loc. cit.*

lyzer; it is found in all tissues, in the female as well as in the male; it gives crystals of haemin with Florence's test, etc., and other reactions peculiar to the adrenal and thyroid principles—both of which are also found in all tissues. A close examination of Masay's report, moreover, does not sustain his opinion that the rise of blood-pressure is to be ascribed to a secretion produced by the pituitary. The rise of pressure was *instantaneous* and general—a fact which points either to vasoconstriction through nerves or to the action of some intensely active and evanescent principle. Both these factors are available. Not only is the pituitary known to be related with the sympathetic system, but Langley¹¹⁵ has called attention to the remarkable fact that “the effects produced by adrenalin upon any tissue are such as follow excitation of the sympathetic nerve which supplies the tissue,” a conclusion confirmed by several observers. This paradoxical fact is clearly explained by the presence of the adrenal principle in the haemoglobin. When Cyon and Masay excited the pituitary, therefore, they merely caused sympathetic constriction of all arterioles, including their offshoots the vasa vasorum; the walls of all vessels receiving an excess of albuminous haemoglobin (adrenoxidase) they contracted, thus causing a rise of blood-pressure.

Again, as is well known, the adrenals are intimately connected with the abdominal ganglia and are, embryologically, sympathetic structures. Their vessels being likewise influenced, a sudden excess of secretion furnished a second cause for the ephemeral rise of blood-pressure observed by Masay. The power of the adrenal secretion to cause such a rise is generally recognized. Schäfer¹¹⁶ characterizes as “astounding” the minuteness of the dose of adrenal extract that will excite physiological effects; 5.7 millionths of a gramme of Abel's epinephrin sulphate to each kilo of body weight was found by Reid Hunt¹¹⁷ to cause a rise of blood-pressure of 66 mm. Hg. As to the action on the heart, Oliver and Schäfer¹¹⁸ found, as is well known, that adrenal products not only acted directly on the muscular walls of blood-vessels, causing them to contract (which accounts for the rise of

¹¹⁵ Langley: *Hill's Recent Advances in Physiology*, p. 584, 1906.

¹¹⁶ Schäfer: *Textbook of Physiology*, I, p. 957, 1898.

¹¹⁷ Reid Hunt: *Amer. Jour. of Physiol.*, v, p. 7, 1901.

¹¹⁸ Oliver and Schäfer: *Jour. of Physiol.*, xvi, p. 1, 1894; xvii, p. 9, 1895

blood-pressure), but also upon the muscular wall of the heart. Finally, the rise of pressure is undoubtedly produced by the adrenalin extract itself, for Strehl and Weiss¹¹⁹ found that clamping of the adrenal veins lowered the blood-pressure, while release of these vessels restored it to its previous level.

Another suggestive fact attesting to the pituitaro-adrenal parallelism is that

The pituitary, in keeping with the adrenals, gives rise to glycosuria.

Adrenal extractives, as observed by Blum,¹²⁰ Croftan,¹²¹ Metzger,¹²² Herter, and others, cause glycosuria. The adrenal secretion evidently provokes the phenomenon also, for Herter and Wakeman¹²³ found that compression of the adrenals, by increasing the outflow of secretion into the adrenal veins, caused glycosuria, while, conversely, adrenalectomy was followed by a marked diminution of the sugar in the blood. Again, we have seen that the adrenal secretion passes from the adrenal veins into the inferior vena cava; Kauffmann¹²⁴ found that when this great vessel was ligated the sugar diminished rapidly, both in the blood and in the urine.

Now, the influence of the pituitary over glycosuria is quite as marked. M. Loeb¹²⁵ urged, over twenty years ago, that the glycosuria which accompanies so often tumors of the pituitary should not be ascribed to mere coincidence. Marie observed it in over one-half of his cases of acromegaly. Borchardt¹²⁶ tabulated 176 patients with this disease, 71 of whom had glycosuria; as I had five years earlier,¹²⁷ he ascribes this symptom to overactivity of the pituitary, and its cessation to final degeneration of this organ. In 16 reported cases studied by Launois and Roy¹²⁸ each subject presented at the autopsy a tumor of the pituitary. That the glycosuria is not due to pressure of the enlarged organ upon the basal or bulbar tissues is shown by the fact that it can be produced in a normal organ. Thus, F. W. Pavy¹²⁹ found that,

¹¹⁹ Strehl and Weiss: Pflüger's Archiv, lxxxvi, p. 107, 1901.

¹²⁰ Blum: Deut. Archiv f. Med., lxxi, Nos. 2 u. 3, p. 146, 1901.

¹²¹ Croftan: American Medicine, January 18, 1902.

¹²² Metzger: Münch. med. Woch., xlix, p. 478, 1902.

¹²³ Herter and Wakeman: Amer. Jour. Med. Sci., January, 1903.

¹²⁴ Kauffmann: Arch. de physiol., viii, p. 150, 1896.

¹²⁵ Loeb: Centralbl. f. inn. Med., September 3, 1898.

¹²⁶ Borchardt: Zeit. f. klin. Med., lxvi, No. 4, 1908.

¹²⁷ Sajous: Loc. cit., i, p. 366, 1st edition, 1903.

¹²⁸ Launois and Roy: C. r. de la Soc. de biol., lv, p. 382, 1903.

¹²⁹ Pavy: Proc. Royal Soc. of London, x, p. 27, 1859.

"of all the operations on the sympathetic of the dog that have yet been performed, removal of the superior cervical ganglion the most rapidly and strongly produces diabetes." This enigmatic result finds its explanation in the light of the conclusions I have submitted: The superior cervical ganglion, as is well known, supplies vasoconstrictor filaments to the pituitary; removal of this ganglion by causing relaxation of its arteries causes the organ to become hyperæmic and therefore overactive, with glycosuria as a result. Control of this conclusion is afforded by the fact that, as in all exacerbations of activity thus induced, the symptom was fleeting, as shown by Pavy's statement that the glycosuria was "only of a temporary nature."

Having now ascertained 1, that the pituitary could alone be the source of impulses to the adrenals; 2, that this organ projected fibers toward the bulb, and, 3, that the pituitary and the adrenals gave rise to similar experimental and clinical phenomena, it became a question whether a nerve-path actually united these organs. Study of this question showed that

The phenomena provoked by both the pituitary and the adrenals can be traced by irritation or sections along a continuous path leading from the pituitary to the adrenals.

The tuber cinereum, which, we have seen, receives fibers from the pituitary, extends backward toward the bulb. Punctures along the upper part of this path by Ott, Tangl, and others not only raised the temperature and quickened the respiration, but a section below the same region by Sawadowsky¹³⁰ and Ott and Scott¹³¹ rendered impossible the production of fever by agents known to produce it. Caselli,¹³² moreover, found that irritation of the same tissues produced glycosuria.

The nerve-path continuing downward, we meet in the pontobulbar region the thermogenic center of Tscheschichin, Schreiber, and Reichert. Suggestive in this connection is the fact that Bruck and Günther¹³³ found that simple puncture with a probe between the pons and medulla not only caused a marked rise of temperature, but that this rise was general. The respiratory center is a familiar classic feature of the medulla; we have

¹³⁰ Sawadowski: *Centralbl. f. d. med. Wissen.*, xxvi, pp. 145, 161, 1888.

¹³¹ Ott and Scott: *Jour. of Exper. Med.*, November, 1907.

¹³² Caselli: *Loc. cit.*

¹³³ Bruck and Günther: *Arch. f. d. ges. Physiol.*, III, p. 578, 1870.

seen how all the phenomena evoked by the adrenals are linked with the respiratory process. All this applies as well to Claude Bernard's puncture in the same region as a cause of glycosuria, and due in the light of all this evidence to irritation of the path from the pituitary to the adrenals.

In the upper portion of the spinal cord, division by Tscheschichin,¹³⁴ Bernard,¹³⁵ and Pochoy,¹³⁶ respectively, in various animals sent the temperature down 7° to 16° C. in from four to twenty-four hours, death following in Pochoy's animals. Riegel¹³⁷ found that production of heat was diminished. That glycosuria is produced through efferent fibers passing downward in the upper cord is shown by the well-known fact, mentioned by Stewart,¹³⁸ that puncture of the bulb does not cause glycosuria if "the spinal cord above the third or fourth dorsal vertebra be cut before the puncture is made."

This level of the cord is of special interest, since it is here that the nerve-path to the adrenals leaves the spinal cord. Here can be evoked a rise of blood-pressure occurring in excess of that due to vasomotor nerves. Thus, François-Franck and Hallion¹³⁹ obtained a rise of pressure by exciting the five upper dorsal rami, and also by stimulating the corresponding segment of the sympathetic chain, although the vasoconstrictor nerves to the organ studied, the liver, was known to reach this organ through a lower ramus, the sixth—a limit confirmed by Langley.¹⁴⁰ But they could not account for this phenomenon. Bulgak, Bunch,¹⁴¹ Jacobi,¹⁴² and others also obtained marked vasoconstrictor effects by exciting these upper rami, although the vasomotor nerves to the organs influenced were known to leave the cord lower down. In other words, a duplicate source of vasoconstriction, as it were, was present whose nature remained obscure. It was brought to light, however, by the fact that Jacobi¹⁴³ found that excessive *inhibitory constriction of the intestinal vessels ceased*, and was replaced by normal vasoconstriction when he severed the nerves

¹³⁴ Tscheschichin: Arch. f. Anat., Physiol., u. wissenschaft. Med., p. 151, 1866

¹³⁵ Bernard: Leçons sur la chaleur animale, p. 161, 1876.

¹³⁶ Pochoy: Thèse de Paris, 1870.

¹³⁷ Riegel: Archiv f. d. ges. Physiol., v, p. 629, 1872.

¹³⁸ Stewart: Manual of Physiology, p. 452, 1900.

François-Franck and Hallion: Arch. de physiol., viii, No. 5, p. 936, 1896.

Langley: Schäfer's Textbook of Physiology, ii, p. 644, 1900.

Bunch: Jour. of Physiol., xxiv, p. 72, 1899.

Jacobi: Arch. f. exper. Path. u. Pharmacol., xxix, p. 171, 1892

¹⁴³ Jacobi: *Ibid.*

to the adrenals. The intense action of their secretion on the blood-pressure clearly accounts, from my viewpoint, for the excessive constriction observed.

Briefly, these facts indicate jointly that

The pituitaro-adrenal path leaves the spinal cord through the upper four or five rami, to enter the sympathetic chain, and then the great splanchnic, which, through the intermediary of the semilunar ganglia, supplies nerves to the adrenals.

That this path is the true one is shown by additional data. Thus, Goltz and Ewald¹⁴⁴ found that animals deprived of their spinal cord from the bulb down could live a long time—years even—but that they showed a striking peculiarity, even after their vessels had resumed their normal caliber, that of dying of cold. Ott¹⁴⁵ found, however, that the animals were able to generate their usual heat when the section was made *below* the fifth dorsal vertebra. This is evidently because the pituitaro-adrenal nerve-paths had left the cord above this level to pass over to the sympathetic chain and the splanchnic, for, although Biedl¹⁴⁶ had failed to increase the secretory activity of the adrenals by exciting electrically all the median and lower dorsal rami, both he and Dreyer¹⁴⁷ had succeeded in doing so by stimulating the great splanchnic nerve. Proof of this is afforded by the fact that the greater splanchnic also transmits impulses to the adrenals which provoke glycosuria, for Laffont¹⁴⁸ caused it by stimulating this nerve. Moreover, it is evidently through a nerve-path starting at least in the medulla that glycosuria is caused; for Eckhard, Kauffmann,¹⁴⁹ and others found that even the glycosuria caused by Bernard's puncture ceased when the greater splanchnic was severed. There can be no doubt that it is through the adrenals that the glycosuria is caused, for, besides the evidence I have already adduced to this effect, A. Mayer¹⁵⁰ found that Bernard's puncture failed to produce this symptom after removal of the adrenals.

On the whole, all the evidence, of which the foregoing is a part, seems to me to have shown:—

¹⁴⁴ Goltz and Ewald: *Archiv f. d. ges. Physiol.*, lxxiii, pp. 362, 400, 1896.

¹⁴⁵ Ott: *Textbook of Physiology*, p. 348, 1904.

¹⁴⁶ Biedl: *Arch. f. d. ges. Physiol.*, lxxvii, No. 9-10, p. 443, 1897.

¹⁴⁷ Dreyer: *Amer. Jour. of Physiol.*, ii, p. 203, 1899.

¹⁴⁸ Laffont, cited by Laulanié: *Éléments de physiologie*, 2d ed., p. 943, 1905.

¹⁴⁹ Kauffmann: *C. r. de la Soc. de biol.*, p. 284, 1894.

¹⁵⁰ Mayer: *Arch. gén. de méd.*, July 17, 1906.

1, *That the pituitary is connected with the adrenals by direct nerve-paths*; 2, *that it thus governs, through the adrenals, general oxidation, metabolism, and nutrition.*

HYPOADRENIA.

This designation is submitted as a more exact one than the term "hypoadrenalism" now increasingly used. The latter suggesting to the uninitiated that the condition it describes is one of habitual insufficiency of the adrenals is misleading, since the secretory activity of these organs is subject at all times, even where advanced lesions exist, to fluctuations. The phrases "insufficiency of the adrenal" and "adrenal insufficiency" portray more acceptably the true condition present, but they are obviously cumbersome and as ill calculated to designate this condition from a scientific standpoint as would "deficiency of red corpuscles" for anemia.

While we owe to Addison, a clinician, the first observations (1855) which indicated that the adrenals were of signal importance to the welfare of the organism, it was Brown-Séquard, a physiologist, who (1856), we have seen, first demonstrated their true importance to life. The symptoms caused by a deficient production of adrenal secretion were not, however, erected to the rank of a special syndrome quite independent of, and capable of occurring without the presence of, Addison's disease, and as a manifestation of other diseases, until Sergent and Bernard¹⁵¹ did so in 1899.

Viewed from my standpoint, however, the symptom-complex of this condition is subject to quite a different interpretation than the prevailing one, all the labors anterior to my own having taken as foundation only two functions: that of sustaining the cardio-vascular tone (Oliver and Schäfer), and that of producing an antitoxic substance capable of neutralizing toxic products of muscular activity, and other undetermined poisons (Abelous and Langlois). The processes through which these effects are brought about having remained obscure, however, more or less empirical conceptions have had to be employed to fill the gaps. Thus, the muscular asthenia in Addison's disease is attributed to the toxic effects of the muscular poisons that the adrenals

¹⁵¹ Sergent and Bernard: *Archives gén. de méd.*, July, 1899.

in their normal state should have destroyed, while, to explain bronzing, irritation of the sympathetic plexuses around the adrenals has to be invoked. The hypothermia, dyspnoea, and other symptoms are indifferently attributed to the low blood-pressure or to the intoxication. If we ask, however, *how* irritation of the sympathetic plexus produces bronzing, or *why* after adrenalectomy the temperature, both rectal and peripheral, steadily declines, or fathom to any depth the explanations that are furnished, it soon becomes apparent that some important factor is missing.

It is this factor which my labors seem to me to have supplied. They afford an explanation of all the symptoms brought on by inadequate functional activity of the adrenals. Being based primarily upon the array of experimental data submitted in the earlier portion of this chapter, they also constitute a foundation for a more exact conception of the various disorders of the adrenals than the prevailing teachings afford.

Another feature which my interpretation of the functions of the adrenals seems to me to elucidate, as will be shown in a special chapter, is the process through which these organs carry on antitoxic functions other than those concerned with toxic wastes of muscular origin. This property, observed by Albanese,¹⁵² who noted a decreased resistance of decapsulated frogs to neurine as compared to normal frogs, was first placed on a solid footing by the researches of Abelous¹⁵³ and Langlois, which showed similar results with atropine in the frog, and strychnine and curare in the rabbit, though less marked. Charrin and Langlois¹⁵⁴ then found that the addition of adrenal extract to nicotine *in vitro* reduced the toxic activity of the latter, and that injected nicotine was also less poisonous when adrenal extract was added to it. Oppenheim¹⁵⁵ then obtained uncertain results with potassium arsenate and atropine, but marked results with phosphorus, guinea-pigs in which the injection of this toxic was followed by that of adrenal extract surviving from two to four times longer in some in-

¹⁵² Albanese: Arch. Italiennes de Biol., pp. 49 and 338, 1892.

¹⁵³ Abelous: Rev. Générale des Sciences, May 15, p. 273, 1893; and Bull. de la Soc. de Biol., April 2, 1898.

¹⁵⁴ Charrin and Langlois: Bull. de la Soc. de Biol., p. 708, 1896.

¹⁵⁵ Oppenheim: Bull. de la Soc. de Biol., March 22, 1901; also "Les Capsules Surrénales. Leur fonction antitoxique," Paris, 1902.

stances, and altogether in others. Strychnine, $\frac{1}{60}$ grain, which killed guinea-pigs in three and four minutes, produced but few spasms and proved harmless as to life when its injection was followed a minute later by one of 2 c.c. of adrenal extract. A larger dose of strychnine ($\frac{1}{48}$ grain) proved fatal, however. These and other experiments with various toxins led Oppenheim to conclude that "the adrenals, which normally destroy poisons elaborated during muscular work, assume great importance during pathological states and must be classed among the most useful of protective organs."

On the whole, in the light of the personal views submitted, hypoadrenia or insufficiency of the adrenals means far more than the effects of lowered blood-pressure and the adequate destruction of muscular wastes; *it means besides: inadequate oxidation and therefore imperfect tissue metabolism and nutrition, and also impairment of the auto-protective functions of the body at large.*

The bearing of this conclusion will be gradually developed while analyzing the three clinical forms into which I have divided hypoadrenia,—a classification which appears to me necessary to enable us to apply prophylactic and remedial measures judiciously. These three forms are the following:—

1. *Functional hypoadrenia*, a form in which the adrenals, though not the seat of organic lesions, are functionally deficient because of tardy development, debilitating influences such as fatigue, starvation, etc., and old age;

2. *Progressive hypoadrenia, or Addison's disease*, a form in which the functions of the adrenals or of their secretory nerves are progressively impaired by organic lesions, tuberculosis, cancer, fibrosis, etc.;

3. *Terminal hypoadrenia*, a form which occurs as a more or less tardy complication of infectious diseases and toxæmias, owing to exhaustion of the secretory activity of the adrenals during the earlier and febrile stage of the causative disease.

FUNCTIONAL HYPOADRENIA.

The adrenals playing so important a rôle in the maintenance of the life process itself, it is obvious that, apart from any organic lesion in these organs, any marked depression of

their functional activity should manifest itself by symptoms corresponding with this depression. To the symptom-complex of this condition I have given the name of "functional hypoadrenia" to distinguish it from the forms due to destructive disorders of the adrenals, which constitute Addison's disease, and offer, of course, a far graver prognosis. As a definition of this condition, I would submit that

Functional hypoadrenia is the symptom-complex of deficient activity of the adrenals due to inadequate development, exhaustion by fatigue, senile degeneration, or any other factor which, without provoking organic lesions in the organs or their nerve-paths, is capable of reducing their secretory activity. Asthenia, sensitiveness to cold and cold extremities, hypotension, weak cardiac action and pulse, anorexia, anemia, slow metabolism, constipation, and psychasthenia are the main symptoms of this condition.

The field covered by functional hypoadrenia is necessarily a vast one, since it includes the asthenias so often met with in the four main stages of life: infancy, childhood, adult, and old age, usually attributed to "weakness" or "exhaustion," and often "neurasthenia," which have been traced to no tangible cause. All I can submit herein, therefore, is a cursory analysis of the subject.

FUNCTIONAL HYPOADRENIA OF INFANCY AND CHILDHOOD.—Although the adrenals are relatively large in the infant (one-third the size of the kidney at birth), their functions are limited to the carrying on of the vital process, at least during the first year of life, the mother's milk supplying the antitoxic products capable of protecting it against the destructive action of poisons of endogenous and exogenous origin. This protective influence of maternal milk is clearly defined in the following quotation from Prof. William Welch's Harvey Lecture: "It is an important function of the mother to transfer to the suckling, through her milk, immunizing bodies, and the infant's stomach has the capacity, which is afterward lost, of absorbing these substances in active state. The relative richness of the suckling's blood in protective antibodies as contrasted with the artificially fed infant explains the greater freedom of the former from infectious diseases." Striking proof of this is

afforded by the fact that during the siege of Paris in 1870-71, according to J. E. Winters,¹⁵⁶ "while the general mortality was doubled, that of infants was lowered 40 per cent. owing to mothers being driven to suckle their infants."

The predilection of children to certain infectious diseases obviously indicates that it is not only in infancy that vulnerability to these disorders exists; it exposes life during the first decade, and more, of the child's existence. If, then, in the infant the maternal milk, as Welch says, protects the suckling against such diseases, at least to a considerable extent, we must conclude that the same underlying cause of vulnerability persists several years, *i.e.*, until it has in some way been overcome. How this occurs we have seen. The adrenals acquire, with other organs, we shall see, the power to supplant the mother in contributing antitoxic bodies to the blood; they supply internal secretions which fulfill this rôle.

These facts point to the adrenals as at least prominent organs among those whose inadequate development explain the special vulnerability of children to certain infections, the "children's diseases." It becomes a question now whether there are degrees of this hypoadrenia which render the child more or less liable to infection.

That degrees of hypoadrenia exist in children is in reality a familiar fact to every physician when the signs of this condition are placed before him. The ruddy, warm, hard-muscled, heavy, out-of-door, romping child with keen appetite and normal functions, is one in whom the adrenals are as active as the development commensurate with its age will permit. He is ruddy and warm because oxidation and metabolism are perfect and the blood-pressure sufficiently high to keep the peripheral tissues well filled with blood; his muscles, skeletal, cardiac, and vascular, are strong because, in addition to being well nourished, they are exercised and well supplied with the adrenal secretion, which, as shown by Oliver and Schäfer, sustains muscular tone. As normal outcome of this state, we have constant stimulation of the functional activity of the adrenals. The muscular exercise and maximum food intake involve a demand for increased metabolism and oxidation, and the resulting

¹⁵⁶ Winters: "Practical Infant Feeding," p. 6.

greater output of wastes imposes upon the adrenals, as participants in the oxidation and auto-protective processes, greater work, more active growth and development, *with increase of defensive efficiency* as normal result.

The pale, emaciated, or pasty child with cold hands and feet, flabby muscles, whose appetite is capricious or deficient—the pampered house-plant so often met among the rich—represents the converse of the healthful child described, just as does the ill-fed, perhaps overworked child of the slums. The emaciation, the cold extremities, indicate deficient oxidation, metabolism and nutrition owing to the torpor of the adrenal functions; the pallor is mainly due to a deficiency of the adrenal principle in the blood and to the resulting low blood-pressure, which entails retrocession of the blood from the surface. This child is not ill, but the hypoadrenia which prevails normally, owing to the undeveloped state of its adrenals, is abnormally low, and it is vulnerable to infection.

That all conditions which in the adult tend to produce functional hypoadrenia affect the child at least to the same extent is self-evident.

FUNCTIONAL HYPOADRENIA IN THE ADULT.—As in the child, the adrenals may be inherently weak. Such subjects do not, as in hypothyroidia, show signs of myxedema; but their circulation and heart action are feeble, they tend to adiposis, and show other signs of hypoadrenia. I have witnessed suggestive bronze spots in such cases. As a rule, however, the development of the adrenals in adults is an accomplished fact—as also that of their coworkers in the immunizing process, the thyroid and pituitary, we shall see. The adrenals, fully capable of sustaining oxidation and metabolism, are able to defend the organism adequately; indeed, they do more: by sustaining oxidation and metabolism up to its highest standard in all organs, they also preserve the efficiency of all other defensive resources, including phagocytosis, with which the body is endowed to their highest level. On the whole, the *normal adult whose adrenals functionate normally is relatively resistant to infection*. The infrequency with which the physician is infected, notwithstanding daily exposure in his professional work, attests to this fact.

Functional hypoadrenia appears, however, when, irrespective

of any disease, and as a result of the vicissitudes of our existence, the adrenals are exhausted by the excessive secretory activity that exaggerated labor or exercise imposes upon them.

Fatigue is a prominent factor in this connection. Mosso's ergograph shows clearly the functional efficiency of the forearm. If by means of this instrument we compare the muscular power of a case of Addison's disease with that of any other kind of sufferer whose muscles are organically normal, a striking difference will be noticed: signs of fatigue appear very soon, and muscular impotence asserts itself where an advanced case of tuberculosis, for example, will be able to show appreciable strength. Intense asthenia is, in fact, a symptom of Addison's disease almost as characteristic as the bronze spots. It is as pre-eminent after experimental removal of both adrenals. This harmonizes with Oliver and Schäfer's demonstration of the influence of the adrenal secretion over muscular tone. Many other proofs could be adduced to show that there is a close relationship between fatigue and the functions of the adrenals. The pale and drawn face of an exhausted man, the readiness with which he suffers from the effects of cold and exposure, especially in the intestines, are familiar features of daily life.

The unusual prevalence of disease among soldiers in the field is of course partly due to the defective sanitation that a campaign entails; but fatigue—particularly that due to heavy marching, carrying heavy accoutrements—is, in my opinion, an important predisposing cause, through its influence upon the adrenals. Not only are these organs called upon to sustain general oxidation and metabolism at a rate exceeding by far that which amply suffices for normal avocations, but the fact that, as shown by Abelous and Langlois,¹⁵⁷ they also serve to destroy the toxic products of muscular activity constitutes another cause of drain upon their secretory resources. "Fatigue," write Morat and Doyon,¹⁵⁸ referring to experimental fatigue in animals deprived of their adrenals, "has an aggravating influence, as first indicated by Abelous and Langlois, and confirmed by Albanese and all authors. Hultgren and Andersson have even

¹⁵⁷ Abelous and Langlois: *Loc. cit.*

¹⁵⁸ Morat and Doyon: "Traité de Physiologie," Art. "Sécrétions Internes," p. 441, 1904.

observed sudden death as a result of powerful movements of the body." Sézary^{155a} has termed "hypoepinephry" a permanent inability of the adrenals to protect the body against infection.

Debility from any source: starvation, loss of blood, etc., as efficiently renders the body vulnerable to disease: "Combine toxin and antitoxin, and inject the mixture," writes Prof. Charrin;¹⁵⁶ "no harm will follow. But weaken the animal by starvation or slight bleeding and administer the same injection; death will follow with all the signs of poisoning by the toxin, with congested adrenals." . . . "That relations exist between the adrenals and infection," urges the same authority, "is today an incontrovertible fact." It follows, therefore, that hypoadrenia from any source should render the body vulnerable to disease. Deficient food, excessive work, that of the sweat-shops for example, account for much of the predilection of those subjected to them to disease.

Masturbation and excessive venery are important morbid factors in this connection. The pallor and asthenia witnessed in these cases, so far unexplained, can readily be accounted for if, as I believe, the liquid portion of the semen is rich in adrenal principle. This is suggested by the fact that spermin, the purest of testicular preparations, gives the same tests and acts precisely as does the adrenal principle. The latter is an oxidizing body acting catalytically; it resists all temperatures up to, and even, boiling; it is insoluble in ether and practically insoluble in absolute alcohol, and gives the guaiac, Florence, and other hæmin tests. Now, spermin not only raises the blood-pressure, slows the heart and produces all other physiological effects peculiar to the adrenal principles, but its solubilities are the same; it gives the same tests; it resists boiling. Moreover, it is regarded in Europe as a powerful "oxidizing tonic" and has been found equally useful in disorders in which adrenal preparations had given good results. The inference that spermin consists mainly of the adrenal product suggests that it is not specific to the testes, but, instead, a constituent of the blood at large; not only did this prove to be the case, but it was found in the blood of females as well as in that of males.

^{155a} Sézary: *Paris médical*, Apr. 20, 1912.

¹⁵⁶ Charrin: "*Les Défenses Naturelles de l'Organisme*," p. 63, Paris,

FUNCTIONAL HYPOADRENIA OF OLD AGE.—Perpetual life would doubtless be ours were it not that all living organic matter is subjected, after more or less precarious periods of growth and adult existence, to one of decline and final disintegration. This applies particularly to the adrenals, if their functions are, as I hold, to sustain oxidation and metabolism, the fundamental processes of the living state. Indeed, the senile state may be said to be as evident in these organs as it is in the features of the aged.

According to Landau,¹⁶⁰ Ecker, Henie, and von Kolliker found that fat occurred in increasing quantities in the adrenal cortex as age advanced, while Hultgren and Andersson found fibrous tissue between the cortex and medulla in very old animals. Minervini¹⁶¹ found a similar condition in the medulla of aged individuals. Dostojewski, moreover, observed a marked—occasionally very great—reduction in the size of the adrenals in the aged. Rolleston¹⁶² has also called attention to this fact. Landau studied the influence of age on the vessels of the adrenals, adopting for the purpose a process introduced by Rauber and applied by many others, including Bezold, Hyrtl, and Lieberkühn, to the study of other organs, viz., injection of the vessels with some hardening substance, and the subsequent use of a corrosion method to destroy the parenchyma. The adrenals receiving their blood through a number of small arteries, the adrenal vein, which contains no valves, was used for the injection. The annexed plate shows the result. The vessels, and therefore the adrenals, are well developed and in full bloom, as it were, in the adrenals of the three young adults, while those of the aged are shrunken and correspondingly deficient as blood-channels—a certain index of the lowered activity of the adrenal functions, and, through these, of the vital process they sustain.

The asthenia of old age thus finds a normal explanation in the defective supply of adrenal secretion—precisely as it does in Addison's disease. In fact, Rolleston states that atrophy of the glands in the young may produce this disease. Lorand,¹⁶³ in

¹⁶⁰ Landau: *St. Petersburg. med. Woch.*, June 14, 1908.

¹⁶¹ Minervini: *Jour. d'anat. et de physiol.*, pp. 449 and 639, 1904.

¹⁶² Rolleston: *Lancet*, Mar. 23, 1895.

¹⁶³ Lorand: "Old Age Deferred," *Am. ed.*, p. 111, 1910.



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his recently published book on old age, urges in fact that "old age is caused by degeneration of the ductless glands, and that there exists a condition of autointoxication in old age" quite in keeping, I may add, with a decline of the antitoxic power shown by the adrenals. Lorand, who has antedated others in showing the influence of the ductless glands upon old age, has found his views confirmed by Campbell,¹⁶⁴ Pineles, Sir Herman Weber and also—though he denies a relationship between old age and myxœdema—Metchnikoff. We shall see in a succeeding chapter, however, that there exists a close connection between the adrenals and the thyroid in the genesis of old age, in the form of a functional relationship.

In his closing remarks on the causation of old age, Lorand remarks: "It is evident from the above considerations that all hygienic errors, be they errors of diet or any kind of excess, will bring about their own punishment, and that premature old age, or a shortened life, will be the result. In fact it is mainly our fault if we become senile at 60 or 70, and die before 90 or 100." Hence the motto of his title page:—

"Man does not die,
He kills himself."

—*Seneca*.

In the light of the data I have submitted, however, it is clear that the lesions to which the adrenals are subjected during infections and autointoxication, from birth to the last day of life, do greatly to shorten it by limiting the functional area of the organs through the local fibrosis they entail. It is quite probable, in fact, that centenarians owe their prolonged longevity mainly to integrity of their adrenals.

Hygiene, and particularly those of its divisions which bear directly upon the prevention of infectious diseases, thus asserts itself as one of the most useful of our sciences in another direction, viz., that of preserving of organism against those diseases which, seemingly benign because they are recovered from, meanles for example, in the end shorten our existence by compromising the integrity of the organs which sustain the vital process itself.

PROPHYLAXIS AND TREATMENT.—Though we are dealing with depraved states of a physiological condition, we cannot

¹⁶⁴ Campbell: *Lancet*, July, 1905.

but regard them as abnormal in the sense that we deem adynamia abnormal and, therefore, susceptible to remedial measures. Indeed, there is much that can be done in each of the three forms of functional hypoadrenia described.

In *infants*, we should by every possible means prevent infection or intoxication to preserve the integrity of their adrenals and other auto-protective organs. The key of the whole situation lies in the fact that, as Rulrüh states, "nearly all the cases and nearly all the deaths are in bottle-fed babies." Physicians are, as a rule, entirely too ready to yield to the demands of social and other claims put forth by mothers who do not wish to nurse their offsprings. The responsibility assumed by both mother and physician under these circumstances is overlooked. I cannot but hope that if this continues, and the sacrifice of countless infants proceeds, laws may be enacted to prevent it by imposing upon the physician the duty of submitting to the State authorities a certificate in which sound reasons shall alone account for his consent to a departure from Nature's methods which entails deaths untold. J. Lewis Smith states that the death rate among foundlings in New York City reached almost 100 per cent. until wet-nurses were provided. Men such as Jacobi, Winters, and many French authorities have written forcibly upon this subject, but seemingly to no avail. The holocaust continues.

Experimental research in the same direction has only served to emphasize the all-important prophylactic value of maternal milk. As L. T. de M. Sajous¹⁰⁵ states: "That milk is capable of conveying antitoxic substances after these have been injected into the mother has been known for a number of years. In 1892 Ehrlich and Brieger demonstrated this fact in their experiments on mice. The offspring of non-immune mice were suckled by other mice which had been immunized against the actions of certain poisons. It was found that the young were thereby rendered immune to the poisons employed, viz., ricin, abrin, and tetanus toxin. This immunity steadily increased during the period of lactation, persisted for some time after, and then gradually disappeared. Ehrlich thus showed that a passive immunity was created in the young by the absorption of milk

¹⁰⁵ L. T. de M. Sajous: Univ. of Penna. Med. Bull., June, 1909.

from an immune adult, and even went so far as to assert that all so-called hereditary immunity was in reality of the passive variety, being transmitted during lactation and not inherent in the offspring itself.

“This transmitted immunity has been shown to occur in various other animals. Thus, in 1893, Popoff showed that immunity against cholera could be transmitted through cows’ milk. He injected bouillon cultures into the peritoneal cavity of a cow and later injected into guinea-pigs from 2 to 10 c.c. of the cow’s milk. The guinea-pigs became immune against cholera. The same observer noted also that when the milk was boiled before injecting it no immunity was produced. Kraus showed that the milk of goats immunized by injections of “typhus-coli bacilli” and cholera organisms had protective and agglutinating properties. He also ascertained that the relative proportion of agglutinating substance present in milk to that contained in the serum was as 1 is to 10. Taking up the subject from the standpoint of tuberculosis, Figari showed in 1905 that the agglutinins and antitoxins of this disease appeared in the milk of cows and goats that had been actively immunized against it. In another series of experiments he fed the milk of immune cows to a number of rabbits, and in others injected it subcutaneously. In both cases these animals, thus passively immunized, were found to transmit to their young, by their milk, the agglutinins and antitoxins of tuberculosis.

“Evidence is not lacking of the transmission of antitoxic substances through human milk. It has long been known that infants below one year of age were but slightly susceptible to certain infectious diseases, and in particular scarlet fever, diphtheria, measles, and mumps. In fact, it was in an attempt to throw some light on this subject that Ehrlich performed his classic experiments on mice in 1892. Four years later Schmid and Pflanz performed some interesting experiments on guinea-pigs. Into some of the animals they injected blood-serum derived from human blood which was taken, at the time of delivery of her child, from a woman to whom had been administered diphtheria antitoxin. Into other guinea-pigs they injected milk from the same woman. The animals were then

given injections of the ordinarily fatal dose of diphtheria toxin. From the results obtained the investigators concluded (1) that antitoxic substances found in the blood of parturient women exist also in the milk; (2) that the quantity of antitoxic substances excreted with the milk is much less than that found in the blood. Similarly, in 1905, la Torre injected diphtheria antitoxin in several wet-nurses, and noted the antitoxic power resulting in the blood of the nurslings by injecting measured amounts of this blood mixed with diphtheria toxin into guinea-pigs. He was able to satisfy himself that a passage of the antibodies occurred in small amounts into the blood of the infants.

"These experiments show, then, that antibodies injected into the mother are transmitted to the offspring. This being the case, it is but reasonable to expect that some of the protective substances ordinarily present in the normal mother's blood should likewise reach the child through the milk. Experiments have shown this also to occur. Moro found that the bactericidal power of the blood-serum in breast-fed children was distinctly greater than in those artificially fed. Further confirmation was afforded by the fact that this difference rapidly disappeared when the bottle-fed infants were put back to the breast."

The prevention of disease in the infant is raised to its highest standard by maternal lactation. The organisms of its gastrointestinal canal are kept under control; the barriers to infection that the respiratory tract and pulmonary alveoli offer are well armed with antitoxic bodies; the blood itself is destructive to pathogenic organisms, and the infant is thus protected against those diseases which, even if recovered from, we have seen, leave enfeebling lesions, fatty and fibrous degeneration, in those organs upon which his health in after years and the duration of his life depend.

In the *child* beyond the nursling period the problem is more difficult. The fatal "second summer" recalls the sins of the milkman, the filth of the cowshed, and of the vessels in which the milk is transported and kept—amply long enough to favor the growth of the oft-present Shiga bacillus, the virulent bacillus coli, and even at times the streptococcus. The correction of these and many other factors replete with danger

to the child, and which surround it on all sides, offers the only resources to diminish not only the mortality of children's diseases, but also their occurrence, besides safeguarding health and longevity in after years. The good already done by our profession in this direction is incalculable. Briefly, public, home, and school hygiene, in the light of the facts I have submitted, not only serves to protect life for the moment when the child is concerned, but its entire career as a healthful individual, while enhancing greatly its chances for a long life.

It now becomes a question whether our resources are such as to enable us to raise, where functional hypoadrenia exists, the autoprotective resources of the child, sufficiently, perhaps, to enable it to resist infection successfully. The influence of many toxins and drugs on the adrenals points clearly to overactivity under their influence. In the first edition of this book, I referred to mercury as occupying "a high position among the stimulants of the adrenal system." Now, C. R. Illingworth¹⁶⁶ and others have found the biniodide of mercury extremely efficient in aborting scarlatina, diphtheria, measles, variola, varicella, pertussis, parotitis, and many other infections. The great vogue of calomel among the physicians of the past generation may have found its *raison d'être* precisely in just such an action—which I have myself observed. Arsenic is a familiar agent in the abortive treatment of malaria in Africa, and, as Surgeon-General Boudin states, in many other diseases. The remarkable results of Petresco with large doses of infusion of digitalis in pneumonia have only been tentatively explained. But if we realize that division of the path to the adrenals arrests and prevents the effects of digitalis, as we shall see elsewhere, there is good ground for the belief that the prevailing conception of the action of this drug is erroneous, and that it is by stimulating the adrenals that it acts, at least in part. In view of the immunizing action of the adrenals, therefore, we can realize how digitalis could be of use in this infectious disease, and how it might prove useful in aborting any pulmonary disorder due to pathogenic organisms. These few examples are submitted merely to show that there is ground for the elaboration of a system of immunizing medication. Its use has served me well.

¹⁶⁶ Illingworth: "The Abortive Treatment of Specific Febrile Disorders," etc., London, 1888.

Very remarkable in this connection is the action of thyroid gland 1 grain (0.06 Gm.), adrenal gland 2 grains (0.12 Gm.), and Bland's pill 1 grain (0.06 Gm.) in a capsule three times daily, previously referred to. Given during meals to a debilitated child of 10 or 12 years it seems promptly to start the vital machinery on a new lease of life—where, of course, the demands of hygiene are adequately met. Meat is of value here, while milk, the fluid portion of which gives the test for oxidase, and which, as shown in the second volume, depends upon the adrenal secretion for its ferment (adrenoxidase), is also of great value. Digitalin or strychnine in small doses is added if the heart is weak or to increase the oxygen intake. All these agents tend, by keeping up a slight hyperemia of the adrenals (and of the other organs acting in conjunction with it), to augment the efficiency of the child's defensive resources.

In the *adult* functional hypoadrenia may have persisted from childhood. Here the measures just suggested for children apply as well not only as preventives where infection threatens, or as abortive treatment, but also to raise the efficiency of the adrenals and the general health of the individual to the normal plane. It is probable that most tonics exert their beneficial influence through the adrenals. That "tonic" doses of mercury, *i.e.*, minute doses, are efficient is well known; we have seen that it is a powerful adrenal stimulant. In toxic doses in fact, as observed by Molin¹⁶⁷, it causes intense congestion and even hemorrhage of the adrenals.

While there is no doubt that meat in excess is harmful, as we shall see under Functional Hyperadrenia, it is no doubt true that, as Lorand¹⁶⁸ states, undernutrition through lack of the necessary proteids in the diet increases the liability to infection, as I urged several years ago in this work. Lorand refers to personal cases of tuberculosis arising from a purely vegetarian diet. On the other hand, Richet and Héricourt¹⁶⁹ obtained remarkable effects from a diet of raw meat in enabling animals to resist tubercle infection by inoculation, and raw meat has become an important factor in the treatment of this disease.

¹⁶⁷ Molin¹⁶⁷: Bulletin général de thérapeutique, Apr. 8, 1906.

¹⁶⁸ Lorand: *Loc. cit.*, p. 313.

¹⁶⁹ Héricourt: *Lancet*, Jan. 7, 1911.

Grawitz¹⁷⁰ also found that a purely vegetarian diet predisposed to anæmia. We have seen that the adrenals supply the blood its albuminous hæmoglobin, a deficiency of which is an important feature of anæmia. Did we live where pathogenic bacteria do not flourish, we might safely undertake to adopt vegetarian principles; but a reasonable amount of meat, by keeping our autoprotective organs, and particularly the adrenals, active, serves a very useful purpose.

The influence of excessive fatigue on the adrenals, we have seen, is such as to weaken greatly their functional activity and, therefore, their oxygenizing and immunizing functions of the blood. The main harmful feature in this connection is the *relative* deficiency of rest, which means, from my viewpoint, inadequate opportunity afforded the adrenals to recuperate. This, of course, should be proportionate to the amount of strain imposed upon these organs, and the resistance of which they are capable. It is probably owing to lack of this that apparently strong men are often the first to "give out" in forced marches. The physical examination being based mainly upon the *status præsens*, and the adrenals being necessarily (for we are now dealing with a new line of thought) overlooked as factors, there is marked inequality in the resistance of the men to strain. This applies as well to the pathogenesis of chronic disorders. In a personal analysis of 40 cases of hay fever, for instance, the severity of the disease corresponded to a considerable degree with the number of children's diseases the patient had had, the worst cases having had six of these diseases in comparatively quick succession.

This suggests the need of ascertaining the number and severity of children's and other diseases to which the recruit has been subjected and to add this factor to others in deciding upon his admission to the service or the arm to which he is to be assigned. The mounted man suffers less from actual fatigue than the infantryman who must carry his accoutrements, arms, cartridges, etc., aggregating in some armies as much as 70 pounds. When, besides, defective or poor food, impure water, exposure, etc., and other frequent accompaniments of a campaign

are taken into account, one need not wonder that disease is a far greater factor as a cause of debility and death than wounds.

Briefly, fatigue should be considered, owing to its inhibiting influence on the adrenals and the immunizing process in which they take part, as an important predisposing cause of disease. The periods of rest should be so adjusted, therefore, as to counteract this by far the most destructive factor of active warfare. In civil life, such hardships are seldom endured, but here likewise much could be done to prevent infection by means calculated to insure the functional integrity of the adrenals.

To stimulate the adrenal functions when marked fatigue prevails would of course only aggravate the hypoadrenia after perhaps a period of temporary betterment. The powdered adrenal substance should, on the other hand, judging from the effects of injections of adrenal extracts in experimentally fatigued animals, serve a useful purpose.

In *old age* the ductless glands assume such importance, that a valuable work has been written by Lorand¹⁷¹ to indicate how the functional activity of these organs could be preserved in order to retard the ravages of age beyond the fifth decade, while prolonging life. The reader is therefore referred to Dr. Lorand's volume for a mass of information which cannot be considered here.

The adrenals, as shown by the plate opposite page 88, are deficient in circulatory activity, and, therefore, unable to sustain functional activity of all organs up to its former standard. It becomes a question whether, realizing this fact, we should by artificial means excite the adrenals to greater activity. That such a step might shorten life instead of prolonging it is probable. In the first place, the frequent presence of arteriosclerosis in the aged counsels prudence; in the second place, to activate the adrenals would only hasten their degeneration by imposing a greater wear and tear upon them. Drugs capable of enhancing adrenal activity had, therefore, better be avoided in the aged.

Far better is it to *compensate* for the loss of efficiency of the adrenals by supplying to the blood, through a suitable diet, substances which contain the adrenal principle. If my opinion

¹⁷¹ A. Lorand: "Old Age Deferred," F. A. Davis Co., Phila., 1910.

that spermin owes its virtues to the adrenal principle it contains is warranted we can understand why Brown-Séquard rejuvenated himself by means of testicular juice injections (I saw him at the time and can testify to its wonderful effects upon him), since he enriched his blood with the *pabulum* of oxidation, metabolism, and general nutrition, without impairing his adrenals. With advanced knowledge we need not follow his example. We have seen that milk contains the adrenal principle, and that all animal tissues owe their functional activity to its presence. In milk, buttermilk especially (since it is almost pure plasma), we have a ready and inexpensive means to compensate for deficient adrenal activity. If debility and other signs of functional hypoadrenia prevail, I advocate the daily addition to the plain, though varied diet to which elderly people should restrict themselves of the expressed juice (uncooked) of one pound of *fresh* beef daily taken in soup, if distasteful otherwise, and salted to taste. This is a powerful agent for good which is well borne by the stomach, and which more than compensates for the weakened adrenals, since it rapidly restores strength and vigor—provided, of course, harmful influences in other directions are avoided, and a hygienic mode of life, with reasonable out-of-door exercise, prevails.

In matters sexual, aged men should be extremely reserved, since the waste of seminal fluid to them means waste of life substance replaced with difficulty and never in abundance.

ADDISON'S DISEASE, OR CHRONIC PROGRESSIVE HYPOADRENIA.

That new lines of thought concerning this disease are not untimely is suggested by Anders's previously quoted statement in a recent edition of his textbook that "the pathologic connection between the symptomatic phenomena of Addison's disease and the anatomic lesions has not been made out."

Of major importance in this connection are the facts that advanced lesions have been found in the adrenals post-mortem, though the subject had during life presented no signs of the Addison syndrome, and that, as Davis¹⁷² states, "in the majority of cases the patients have complained of asthenia for a consider-

¹⁷² Davis: *Sajous's Cyclopædia of Prac. Med.*, vol. 1, p. 132, 3d ed., 1900.

able time prior to the appearance of noticeable pigmentation on the surface." Many cases die, in fact, before the pigmentation appears. Under these circumstances it is evident that the prevailing teaching that bronzing is the characteristic sign of Addison's disease—raised to the dignity of a *sine qua non* in some works by the dictum "without bronzing, no Addison's disease"—is an unfortunate one for the patient's welfare, since, as shown elsewhere in this work, bronzing is a symptom denoting advanced lesions of the adrenals or in the course of their secretory nerves, whether in the ganglia or the splanchnic, or even the spinal cord from which the adrenal paths originate. It is because of the presence of these nerves in the abdominal sympathetic (the greater splanchnic in particular, as demonstrated by Biedl¹⁷³ and Dreyer¹⁷⁴), was not known to Martineau,¹⁷⁵ Jaccoud, Lancereaux,¹⁷⁶ von Kahlden,¹⁷⁷ and others that they denied that the adrenal insufficiency was always the underlying cause of the disease, as held by Addison himself, Gull, Trousseau, and many other of the older clinicians. It is apparent that a lesion anywhere in the course of these nerves must be capable of causing inhibition of the adrenal functions and Addison's disease, by interfering both with the secretory activity of the glands and the formation of their secretion. This is well exemplified by cases reported by Semmola and Brault in which bronzing was due to pressure upon the semilunar ganglia and the solar plexus; the flow of impulses through these structures to the adrenals being impeded, the functions of these organs were inhibited. Pressure or organic lesions may occur anywhere in the pituitaro-adrenal nerve-path. Even the cachetic stage of acromegaly is often attended by a bronze pigment "strongly resembling that found in Addison's disease" we have seen. From my viewpoint, therefore,

Addison's disease is the symptom-complex of progressive hypoadrenia, i.e., of insufficiency of the adrenals. It occurs when, owing to progressive organic lesions in these organs or in the course of their secretory nerves (the abdominal sympathetic and its ganglia, the spinal axis or the pituitary body), the

¹⁷³ Biedl: *Loc. cit.*

¹⁷⁴ Dreyer: *Loc. cit.*

¹⁷⁵ Martineau: Thèse de Paris, 1864.

¹⁷⁶ Lancereaux: *Archives de Médecine*, Jan., 1890.

¹⁷⁷ Von Kahlden: *Archiv f. Anat. u. Phys.*, Bd. cxlv.

adrenal secretion produced is increasingly inadequate to sustain general oxygenation, metabolism and nutrition, and the cardiovascular tone.

PATHOGENESIS AND SYMPTOMATOLOGY.—These will be considered together to indicate the intimate relationship between them when the functions of the adrenals are interpreted from my viewpoint. This will be further facilitated by analyzing the symptoms in their physiological sequence.

Hypothermia, Coldness, and Dyspnea.—These symptoms are self-evident results of deficient oxygen intake, and of the correspondingly deficient oxidation and metabolism incident upon the deficiency of adrenal secretion. The sensation of cold is aggravated by the fact that the deficiency of the latter—or rather of the adrenoxidase it becomes—entails relaxation of the arteries and a low blood-pressure; the blood accumulating in the larger trunks of the splanchnic area, the peripheral vessels are partially depleted of theirs, and peripheral oxidation being thus diminished from two directions, the patient complains of chilliness. The dyspnea is due to the same two factors: inadequacy of adrenal secretion to properly oxygenize the blood, and ischemia of the lungs through retrocession of the blood into the deeper vessels. An aggravating factor is the intense muscular weakness which also, of course, affects the thoracic respiratory muscles.

Progressive Asthenia, Weak Heart Action, and Vascular Hypotension.—Oliver and Schäfer and, later, Cybulsky and Szymonowicz having found, we have seen, that the adrenal secretion sustained the tone of the cardiovascular and skeletal muscles by a direct action upon them, a process supplemented, as I have shown, by its power to sustain oxidation and metabolism in these (as well as all other tissues), it is obvious that deficiency of this secretion should produce weakness of all muscular tissues, *i.e.*, loss of contractile power. Asthenia, weak heart action, and relaxation of the arteries—the blood-pressure sometimes being as low as 50 mm.—are thus a direct result of the adrenal insufficiency. Here again, however, the low vascular tension aggravates the morbid process by causing retrogression of the blood toward the deeper channels of the splanchnic area. The cardiac and skeletal muscles receiving an unusually small volume of blood, their contractile power is weakened in proportion and their

resistance to fatigue reduced practically to *nil*. Sergeant has proposed a diagnostic sign, "the white line," which I would explain by this peripheral ischæmia, is obtained by lightly rubbing the surface of the abdomen with the pulp of a finger. A broad, white streak soon appears, which gradually becomes more distinct, then after three or four minutes fades away.

Emaciation, Anorexia, Vomiting, Diarrhœa.—That deficient oxidation and metabolism, upon which nutrition depend, should entail emaciation is self-evident. Anorexia is but a consequence of this state of affairs, the utilization of less foodstuffs being a normal result of deficient demand for the same by the tissues. The vomiting is due mainly to the gastropnoxis caused by relaxation of the muscular coat of the stomach, a condition similar to that present in all other muscles of the body. Vomiting occurs when imperfectly digested materials accumulate in the stomach, partly because of its dilatation and partly as a result of deficient peristaltic action from the same muscular incompetence. A corresponding degree of asthenia of intestinal muscles also entails constipation owing to deficient peristalsis in certain cases, while in others, or subsequently, there is diarrhœa owing to relaxation of the intestinal arterioles and the resulting passive congestion of the intestinal mucosa.

Bronzing.—Langlois, Gourfein, and others have found that one-eleventh of the adrenals sufficed to carry on their functions; this illustrates the small proportion of adrenal secretion required and the progress any local lesion may make before the organism at large is morbidly influenced. Vassale and Zaufrognini¹⁷⁸ found that if all but a small fraction of the medulla is left in experimental animals, all the typical signs other than pigmentation may appear. This illustrates the valuelessness of Nothnagel's observation that pigmentation did not occur in 153 animals from which he had removed both adrenals. Death occurred in all these animals long before bronzing had had time to occur. Boinet, who, on the other hand, utilized rats, which are known to survive the operation longer than any other animal—owing to the frequent presence of accessory organs—observed typical pigmentation in all animals which had had several months' postoperative life. Tizzoni noted

¹⁷⁸ Vassale and Zaufrognini: *Riforma Medica*, Oct. 31, 1902.

similar results after crushing the organs; Brown-Séquard, in fact, had long before noted that bronzing appeared in animals in which the operation did not prove fatal for some months, the other symptoms present being analogous to those of Addison's disease. It is because of these and other facts adduced in the earlier editions of this work that I concluded¹⁷⁹ that "*insufficiency of the adrenals only manifests itself by bronzing when, from any cause, all but a small proportion of the organs has been rendered physiologically inactive.*" Briefly, the bronzing of Addison's disease occurs only in advanced hypoadrenia.

We have seen that the pigment which gives the skin and the mucous membranes their bronze hue is mainly composed of the adrenal product, or adrenoxidase, which, from my viewpoint, is the oxidizing body of the hæmoglobin.¹⁸⁰ That the pigment was a product of the adrenals was first suggested by Brown-Séquard. But why should it, though a constituent of the circulating blood, accumulate in the tissues? Here, again, two factors prevail: the extremely weak blood-pressure in advanced cases, and the identity of the adrenal product as the albuminous constituent of hæmoglobin. The *vis a tergo* motion of the blood being slowed, the plasma circulating in the cutaneous capillaries is increasingly unable to traverse these minute vessels and is deposited in the rete mucosum. The adrenal constituent being freed, it resumes its original reducing power and undergoes the changes of color witnessed when fluid-extracts of adrenal substance are exposed to the air and light—a yellowish brown gradually turning to bronze and often to black. It is because of this that bronzing is not characteristic of Addison's disease, and that it occurs in other cachectic disorders.

This does not militate against the production of bronzing by other factors, local irritation, drugs, cutaneous or nervous disorders. It explains only its mode of production in Addison's disease, as I interpret it.

Lumbar and abdominal pain often occurs early in the disease, but may be absent through its entire course. The fact that it occurs suddenly in crises points to pressure upon the

¹⁷⁹ See 1st, 2d, or 3d ed., p. 86.

¹⁸⁰ This question is treated in full on p. 835.

abundant nervous structures in the immediate neighborhood of the adrenals or through dilatation of these organs when the general blood-pressure, from any intercurrent cause, becomes high. The intense congestion attending or preceding adrenal hæmorrhage, which often terminates Addison's disease, suggests that a temporary exacerbation of the local hyperæmia incident upon the local lesion is the main cause of this symptom.

Tendency to Syncope, Impairment of Vision, and Hearing.—

The tendency to syncope is such in some cases that elevation of the head sometimes suffices to cause death. Not only is this accounted for by the low blood-pressure and the resulting cerebral ischæmia, but also by the poverty of the blood in adrenoxidase, its oxidizing principle. The extremely small, soft, compressible, and sometimes imperceptible pulse bespeaks a third factor in the pathogenesis of this symptom: great systolic weakness of the heart, owing to loss of the direct support received from the adrenal secretion in transit through its right auricle and ventricle, and deficient metabolism in the left myocardium.

The same cerebral ischæmia and anæmia which predispose to syncope and vertigo also affect the organs of special sense; hence the impaired vision and hearing.

Headache, Irritability, Hallucinations, Delirium, Convulsions.—We have seen that, as shown by Abélous and Langlois, the adrenal secretion is endowed with antitoxic functions. It follows, therefore, that any adrenal disorder capable of materially reducing the supply of this secretion must lead to accumulation of the tissue poisons it is known to destroy. It is these poisons that give rise to headache, irritability, muscular twitching, rigidity, delirium, and convulsions similar to those witnessed in puerperal eclampsia, also due to endogenous poisons.

Coma, Sudden Death.—Gradual decline with profound asthenia, or some intercurrent disorder and coma often terminates the case, but not infrequently death occurs in the midst of a convulsion, or suddenly without such, owing to adrenal hæmorrhage. This is due to the accumulation of poisons referred to under the preceding heading. By irritating or exciting the vasomotor center, these poisons cause a rise of blood-pressure and even fever. The remnant of medulla in the adrenals and their intrinsic sinusoidal vessels, medullar and cortical, being

subjected to inordinate pressure, suddenly rupture, constituting what Arnaud has very aptly termed "adrenal apoplexy."

TREATMENT.—The only curative measure worthy of any confidence is one calculated to replace the destroyed glands or, at least, to supply the organism with the adrenal product in some form.

The grafting of adrenals into the tissue has led to such unfortunate results that Courmont, after a personal experience in the use of this procedure, declared it formally contraindicated. Indeed, Bra,¹⁸¹ after grafting the suprarenals of a dog into the cellular tissue of the abdomen in a child of 14 years, witnessed its death in three days. Jaboulay,¹⁸² having resorted to the same method in two cases, lost both within twenty-four hours, owing, he honestly admits, to the operation. The same result followed in Courmont's case. If this question is closely analyzed, however, it becomes apparent that it is not the method proper, or the operators, that are responsible for the untoward results, but rather the fact that the functions of the adrenals were still too obscure, at the time the operations were performed, to afford the indications necessary for a judicious adjustment of the quantity of adrenal tissue grafted to the needs of each particular case.

The cause of death in such cases is made clear by my interpretation of the functions of the adrenals. Thus Courmont, referring to the three cases in which dog's adrenals had been grafted in cases of Addison's disease, writes: "In the three cases the results were disastrous. In my own case the patient died in twenty-four hours with a *formidable hyperthermia* and cardiac collapse," while specifying that there was no infection of the wound. With the adrenals as the source of a secretion whose mission is to sustain oxidation, the cause of the excessive temperature is self-evident. The grafted adrenal tissues furnished adrenal substance far in excess of the needs of the organism, and the phenomena produced were those of the physiological function carried out by the secretion, but "formidably" exaggerated.

If grafting is resorted to, the proportion of tissue employed

¹⁸¹ Bra: Cited by E. X. Adams, *Practitioner*, Oct., 1903.

¹⁸² Jaboulay: *Lyon Médical*, Mar. 21, 1897.

should be adjusted to the needs of each case, always beginning with a small quantity of tissue and adding small grafts until distinct improvement is noted. It must be said, however, that the experimental use of small grafts has not, so far, been attended with much success.

Indeed, it has not been possible to obtain successful grafts in a sufficiently large proportion of experimental animals so far to warrant grafting in man. Dominicis,¹⁸³ Boinet, Imbert,¹⁸⁴ Coenen,¹⁸⁵ Taddei and Torrini,¹⁸⁶ and others had unsuccessfully attempted to introduce grafts in various parts of the body. Abelous,¹⁸⁷ however, succeeded in preserving life in animals from which the adrenals had been removed by means of grafts; but subsequent degeneration of the latter caused death. Gourfein met with similar results. Haberer,¹⁸⁸ after partly detaching one adrenal in such a way as to provide a pedicle which would continue to supply the organ with blood, inserted the free segment in a slit in the kidney. This operation, tried in 86 animals, proved successful in 50 per cent. But to replace a diseased organ, transplantation of a normal organ obtained from another subject or lower animal is necessary. The nearest approach to this result was that obtained by Busch, Leonard, and Wright,¹⁸⁹ who succeeded in transplanting the adrenal of one rabbit into the kidney of another which had also been deprived of one adrenal. On removing the remaining adrenal thirty-six days later, the animal recovered, showing that the implanted adrenal was functionally active. On removing the kidney containing the grafted adrenal twenty-nine days later, however, the animal died in forty-three hours. On the whole, it has become apparent that the kidney is the best structure for the implantation of adrenal grafts, and that it is in this direction that our attempts at grafting should be directed. Recalling the experience of Jaboulay, Courmont, and others to the effect that the dog's adrenal produces fatal hyperthermia, the organs of smaller animals might be used, adding one or more subsequently if need be.

Dominicis: *Gazetta degli Osp. e. d. Clin.*, Nov. 22, 1896.

Imbert: *Le Bulletin Médical*, Nov. 8, 1899.

¹⁸⁵ Coenen: *Arch. f. klin. Chir.*, B. lxxxi, Hft. 2, 1907.

¹⁸⁶ Taddei and Torrini: *Lo Sperimentale*, July-Aug., 1907.

Abelous: *C. R. de la Soc. de Biol.*, Nov., 1892.

Haberer: *Arch. für klin. Chir.*, B. lxxviii, No. 2, 1908.

¹⁸⁹ Busch, Leonard, and Wright: *Jour. Amer. Med. Assoc.*, Aug. 22, 1908.

As to the general results of adrenal preparations and grafting, a series of 120 cases collected from literature within my reach, including 97 previously collected by E. W. Adams,¹⁹⁰ in all of which adrenal preparations had been used in some form, gave the following results:—

1. Cases in which death can be ascribed to grafting or adrenal preparations	8
2. Cases in which the benefit was slight or nil	51
3. Cases in which marked improvement occurred	36
4. Cases in which permanent benefit was obtained ..	25

120

The unfavorable results obtained with adrenal preparations given orally are doubtless due, in a great measure, to their empirical use, and regardless of the dose indicated in each case. E. W. Adams¹⁹¹ refers to a group of 7 cases, "in which alarming or fatal results were presumably or possibly due to the treatment." He mentions, for instance, 2 cases reported by Affleck¹⁹² treated with "suprarenal gland extract." The chart notes include the words: "Alarming collapse. One of the cases began to improve markedly when the extract was stopped." In the original paper, reference is made to another case treated by suprarenal extract in which "similar collapse was noted." The dose was not mentioned. Such cases are apt to be regarded as examples of the sudden death observed in Addison's disease, to which Addison himself, Dieulafoy, Anderson, Bradbury, and others have called attention. Guiol,¹⁹³ having observed similar signs of intoxication and collapse, tried the remedy in a normal subject and obtained the same morbid phenomena. The essential feature in carrying out this mode of treatment is to *adjust the amount administered to the needs of each case*. Addison's disease being due, from my viewpoint, to inadequate oxygenation and metabolic activity, the results in turn of a deficient production of the adrenal secretion, it follows that *the temperature and blood-pressure indicate the*

¹⁹⁰ Adams: Practitioner, Oct., 1903.

¹⁹¹ Adams: Loc. cit.

¹⁹² Affleck: Lancet, Dec. 31, 1898.

¹⁹³ Guiol: Bull. de la Soc. médico-chi. du Var, Dec., 1906.

degree to which the adrenals are still performing their functions. It is plain, therefore, that our aim should be *to supply only just enough adrenal extractive to compensate for the deficiency of adrenal secretion produced.*

This may be illustrated by the history of 25 cases of Addison's disease in which, out of the 120, permanent benefit occurred. In 1 of these, treated by Bate,¹⁹⁴ but $\frac{1}{12}$ grain (0.005 Gm.) of adrenal extract three times daily caused very great and lasting improvement with marked lessening of the bronzing. When the remedy could not be obtained temporarily, which occurred twice, the case relapsed. Conversely, Suckling¹⁹⁵ began with 10 grains daily in another case and gradually increased until 175 grains were given each day; he also obtained favorable results. That in Bate's case the adrenals were still able *almost* to carry on their function is self-evident, while in Suckling's the remedy practically compensated for the adrenals; the local morbid process in them was still active, and such as to paralyze their functions—a fact which was well shown by the severity of the case when the use of the extract was begun. The average dose is probably that used by Weigall¹⁹⁶ in a very severe case—5 grains, increased to 10 grains, of the extract three times a day. The patient increased 6 pounds in two weeks, and after about three months 56 pounds. In other words, in the 25 cases of permanent benefit, although the remedy was used empirically, it so happened in all probability that *the doses employed coincided with the needs of the organism.* In the 51 cases in which no benefit was obtained several occur in which failure was evidently due to inadequate dosage or to too early cessation of the treatment, while in others excessive doses—practically in every instance a too rapid or excessive increase of the dose—as clearly prevented a successful issue.

Excessive doses may not only raise the temperature beyond normal, as we have seen, but they may also, by increasing general oxidation and metabolism, so increase the functions of the thyroid that we may have, besides, symptoms of exophthalmic goiter. Boinet¹⁹⁷ reported such a case in a patient who had

¹⁹⁴ Bate: Amer. Pract. and News, Aug. 1, 1899.

¹⁹⁵ Suckling: Brit. Med. Jour., May 28, 1898.

¹⁹⁶ Weigall: Australasian Med. Gaz., Oct. 20, 1905.

¹⁹⁷ Boinet: C. R. de la société de biol., n. 891, 1889.

increased the dose of his own accord. The same clinician¹⁹⁸ observed sudden death in 2 cases after injecting $\frac{1}{180}$ grain of adrenalin, the rise of pressure having produced, doubtless, hæmorrhagic destruction of what remained of adrenal medulla.

Adrenalin or any active principle of the epinephrin group should not be used in the disease owing to the suddenness with which they elevate the blood-pressure. They prove effective, sometimes, when given by the mouth, 7 to 8 drops of the 1:1000 solution being given daily. Boinet¹⁹⁹ recently reported 3 such cases, while in 4 cases the same treatment proved useless. Supracapsulin (Cudahy) might prove more efficient than adrenalin owing to the claim that it is not oxidizable because it contains 0.5 per cent. of chloral. The dried gland (the *glandulæ suprarenales siccae* of the U. S. P.) is available in tablet form, 1 grain representing about 5 grains of the fresh gland. If the blood-pressure and the temperature are considerably below normal, 3 grains (0.2 Gm.) may be given to an adult twice daily during meals, from the start and kept up and increased if need be until they become normal, regulating the dose thereafter so as to maintain this level. Smaller doses are indicated if the blood-pressure and temperature do not depart much from the normal. The powder is sometimes to be preferred in the same doses, owing to the possibility of administering it in capsules which conceal the rather unpleasant odor of adrenal gland. Unfortunately no very reliable preparation is yet available.

Glycerin extract of fresh gland may be prepared where the desiccated gland cannot be obtained; or the fresh mutton or beef gland may be given twice daily, in doses of 5 to 15 grains, with the food. The glycerin extract is also used hypodermically, but the injections are painful and are no more effective than the dried gland.

As previously stated, I ascribe the therapeutic effects of pituitary extract to the adrenal principle it contains. It is indicated, therefore, in Addison's disease. The best way to administer it is by intramuscular injections, using 15 minims (1 c.c.) of the preparation termed "vaporole" by Burroughs Well-

¹⁹⁸ Boinet: Arch. générales de méd., Feb. 9, 1904.

¹⁹⁹ Boinet: Bulletin de l'Acad. de Med., Oct. 5, 1909.

come and Co. and supplied in small vials containing the above quantity. The dose should be renewed as frequently as needed to raise the temperature to normal and keep it there.

Pitres and Gautrelet²⁰⁰ found recently that the use of glucose, to compensate for the deficient formation of glycogen (due to inadequate conversion of starches into this substance), caused the intense adynamia and sensation of fatigue to improve materially, especially when given simultaneously with adrenal preparations.

Iron in the form of Bland's mass is of advantage to counteract the anæmia. The adrenal product, by increasing the albuminous hæmoglobin, requires the iron to build up hæmatin and the complete hæmoglobin. It is indicated even when the blood-count, which may be very low, as noted by Hayem, shows but little diminution of red corpuscles. One grain of iron can be given with desiccated adrenal powder in capsules. Other drugs should be used with great circumspection, especially in advanced cases. Strychnine, digitalis, and other drugs which raise the blood-pressure expose the patient to adrenal hæmorrhage.

The intense asthenia, the tendency to syncope on exertion, and the weakness of the heart impose the need of remaining as quiet as possible. When the case is advanced, rest in bed is indicated. Nutritious, but readily digested food tends to delay the morbid process, meats and milk contributing their own adrenal substance to compensate in a measure for the patient's inadequate supply. Lavage of the stomach affords considerable relief in cases in which there is gastroptosis and retention of food materials as a result of relaxation of the muscular coat of the stomach, in keeping with the adynamia of all muscular elements. Bismuth is the safest agent to use for the diarrhœa in conjunction with the adrenal preparation employed.

When Addison's disease is due to tuberculosis of the adrenals, as is usually the case, the carbonate of creosote 5 grains (0.3 Gm.) three times daily may advantageously be given with the adrenal preparation. The iodides, which do not raise the blood-pressure, have been used with advantage.

²⁰⁰ Pitres and Gautrelet: *Revue de Thérap. Médico-Chir.*, Aug. 15, 1910.

TERMINAL HYPOADRENIA.

For reasons given on page 80, the term "hypoadrenia" was introduced in lieu of those at present in vogue, which are either incorrect or cumbersome. Interpreted from my viewpoint,

Terminal hypoadrenia is that form of adrenal insufficiency which occurs late in the course of an acute febrile disease, as a result of the exhausting secretory activity, probably aggravated by temporary local lesions to which the adrenals are subjected, as defensive organs, during the febrile period of the disease. It should be clearly differentiated from intercurrent hyperadrenia, a more dangerous type, considered beyond, which may appear at any time in the course of an acute infection or toxæmia.

The adrenals being admittedly concerned in the protection of the organism during infections and intoxications by contributing an excess of their secretion during the febrile stage of the disease (sometimes considerably prolonged), it follows that after this stage is over the adrenals should lapse into a condition of more or less temporary insufficiency through fatigue or exhaustion. This effect is well exemplified by the recent observation of Carl^{201a} that the adrenals of frogs after strychnine convulsion and also of a bicyclist who had died of extreme exertion no longer gave the chromaffin reaction.

In lobar pneumonia and bronchopneumonia, for instance, resolution may be considerably delayed and convalescence likewise. There is, late in the case, extreme adynamia and a low blood-pressure, the temperature is below normal, the pulse weak and more or less rapid, and death from heart-failure is not infrequent. In typhoid fever, hypoadrenia is commonly observed. The disease assumes what is now known as the cardiac type, with weak pulse, prostration, a tendency to fainting. A case of this class, and which shows clearly the adrenal involvement, was recently described by Josué.²⁰¹ Here, again, we find, late in the case, extreme prostration, a rapid, weak and sometimes irregular pulse, hypothermia, and a marked tendency to vertigo, fainting, and cardiac failure. Are these phenomena due, in keeping with the effects of poisons on the adrenals

²⁰¹ Josué: Société Médicale des Hôpitaux, May 21, 1909.

^{201a} Berliner klin. Wochenschrift, June 12, 1911.

already described in these pages, to vascular lesions of these organs? Sicard²⁰² reported the case of a young woman in whom the foregoing symptoms appeared on the ninth day of a broncho-pneumonia. Extreme muscular weakness, marked hypothermia and low blood-pressure, diarrhœa, and Sergeant's white line were present. On the fifteenth day the blood-pressure fell to 70 or 80 (7 or 8 per cent. Potain) and death followed three days later. At the autopsy the adrenals were found hæmorrhagic. This suggests that adrenal lesions may be present in all such cases. Yet, Ribadeau-Dumas and Bing²⁰³ have witnessed the same symptoms in cases of measles which recovered, while Bossuet²⁰⁴ refers to 8 cases in various febrile disorders in which typical symptoms of adrenal insufficiency, asthenia, low blood-pressure, etc., developed suddenly and disappeared spontaneously, aided perhaps by adrenal extract which had been administered. What organic lesions occur in such cases, therefore, are not necessarily fatal, as emphasized by the areas of fibrosis (old healed lesions) often found at autopsies.²⁰⁵

As stated recently by Morichau-Beauchant,²⁰⁶ the adrenals seem to show a special predilection for certain infections. Diphtheria easily leads them all in this connection. So seriously do these organs suffer in these cases that Sevestre and Marfan have termed the type "secondary syndrome of malignant diphtheria." Hutinel ascribes the fulminating cases of scarlatina to this cause. Tetanus, erysipelas, mumps, certain forms of tonsillitis, and certain streptococcic infections are occasionally witnessed which also present the typical syndrome of hypoadrenia. Goldzicher²⁰⁷ was led by his researches to conclude that in the various forms of septicæmia the appearance of lower blood-pressure was to be ascribed to insufficiency of the adrenals. Finally, Comessatti^{207a} found that in diseases of long duration, the adrenalin contained in the adrenals was far less than in those of subjects in which death had occurred suddenly.

PATHOGENESIS AND SYMPTOMATOLOGY.—These two features of terminal hypoadrenia have been partially covered in the

²⁰² Sicard: Bulletin de la Soc. Médicale, July 21, 1904.

²⁰³ Ribadeau-Dumas and Bing: Bull. de la Soc. Anat., June 3, 1904.

²⁰⁴ Bossuet: Gazette hebdomadaire de Sc. méd. de Bordeaux, Oct. 30, 1904.

²⁰⁵ Loeper and Oppenheim, in Malad. des Reins et des Caps. Sur., by Debove, etc., p. 738, 1906.

²⁰⁶ Morichau-Beauchant: Le progrès médical, Oct. 9, 1909.

²⁰⁷ Goldzicher: Wiener klin. Woch., June 10, 1910.

^{207a} Comessatti: La Clinica med. Italiana, Nov., 1910.

foregoing lines. Briefly, if at the end of an infectious disease the case, instead of proceeding to convalescence, remains in a condition of asthenia, with low blood-pressure and temperature, there is good ground for the conclusion that this form of hypoadrenia has occurred. Exhaustion of the adrenals during the acute process having inhibited their secretory activity, the above symptoms result from inadequate oxidation of, and metabolic activity in, the tissues. Sergeant's white line, already described, may be obtained in the majority of these cases. The patient complains of chilliness, the surface is pale owing to the poverty of the blood in cellular elements and hæmoglobin, and to recession of the blood-mass from the surface to the deeper vascular trunks. The vascular tension being low the pulse is rapid and the heart-beat weak. Anorexia due to deficient metabolism and diminished nutritional needs, nausea, the result of relaxation of the gastric muscular coat, and diarrhoea due to a similar condition of the muscular coat of the (already passively engorged) intestine, more or less frequent fainting spells may all be witnessed in such cases, which are always greatly exposed to relapse or to sudden demise from heart-failure.

Complications of various kinds may occur. The immunizing processes being greatly weakened through the deficiency of adrenal secretion, one of its important factors, septic infection, abscesses, bone lesions, tuberculosis of a rapid type, and other infections may more or less rapidly develop. Disorders of nutrition, cholelithiasis, and occasionally Addison's disease may also appear. In acute pulmonary infections, pneumonia, for example, tissues in the neighborhood of the focus of infection, the pleura, the heart, etc., inadequately protected by the blood or its phagocytic cells become infected. Briefly, the body is rendered vulnerable to the attacks of almost any pathogenic organism.

PATHOLOGY.—In the special type in question no adrenal lesion may be discernible. In the majority of instances, however, the organs are enlarged and congested, and may show here and there a limited hæmorrhagic area. Their appearance suggests not only the conditions incident upon functional exhaustion, but the presence of a *passive* congestion (see page 34) resulting from loss of resiliency of their sinusoidal vessels, thus

impeding the circulation through them. Occasionally they are the seat of suppuration, a complication which is apt to be observed when the causative disease is, or includes, a streptococcic infection, pneumonia or meningitis.

The pathological picture of the more severe form of adrenal complication, *i.e.*, intercurrent hyperadrenia, considered beyond, shows far more distinct lesions of the adrenal parenchyma. Hence the typical lethal phenomena that attend many of these cases.

TREATMENT.—In these particular cases opotherapy, or rather the use of adrenal gland, or of pituitary body, which acts very similarly, but with less violence and more lasting effects, sometimes gives surprising results. The adrenal product—which from my viewpoint is also the main active agent in the neural lobe of the pituitary, as shown by the chromaffin test—supplies precisely what the body needs, *e.g.*, the resumption of all oxidation processes, which means general metabolism and nutrition, and the resulting rise of blood-pressure, which causes the blood to circulate normally in all organs, including the skin, and in the adrenals themselves. Indirect effects are also obtained: its action on the heart increases the contractile power of this organ, and, being thus rendered capable of projecting the blood with more vigor through the lungs, oxygenation of the blood becomes more perfect—a process materially aided by the rise of blood-pressure, which, as stated, drives the blood from the splanchnic area toward the peripheral organs, including the lungs and the brain. From these features alone, considerable benefit is derived. If we recall, moreover, the participation of the adrenal secretion (which the adrenal preparation administered represents) in the immunizing process, we have the added factors of ridding the blood of any intermediate—and therefore toxic—wastes, bacterial toxins, etc., it may contain, and of increasing phagocytic activity, thus antagonizing efficiently any pathogenic organism that may remain to compromise the issue. Thus explained, we can understand the phrase “little short of marvelous” applied to the results obtained by some clinicians. We can also understand the marked reduction in the mortality obtained by Hod-

dick²⁰⁸ in cases of peritonitis following appendicitis accompanied by uncontrollable decline of the blood-pressure, cyanosis, and other evidences of collapse, and also in puerperal toxæmias, by the slow intravenous use of adrenalin in saline solution. Hoddick ascribes the lowering of the blood-pressure to paralysis of the vasomotor center; but as the toxæmia is the cause of this condition, an agent capable of counteracting both cause and effect is necessary. This is met by the adrenal principle. Josué,²⁰⁹ in typhoid fever, likewise relieved threatening symptoms by injecting 15 minims (1 c.c.) of adrenalin (1:1000 sol.) in $\frac{1}{2}$ to 1 pint (250 to 500 c.c.) of physiological saline solution subcutaneously. The influence of the saline solution in these cases must not be overlooked, however. Seven years ago, I urged that death was often due, in infectious and septic diseases, to deficient circulatory osmosis, and advised the use of saline solution *from the onset* in all febrile diseases. Netter²¹⁰ has used large doses of the adrenal active principle with profit. Marran and Darré²¹¹ found it of great value in the collapse of diphtheria with marked asthenia, low blood-pressure, and subnormal temperature. Moizard²¹² recommended adrenal opotherapy as soon as asthenia and low blood-pressure occur in any infection. He gives daily two fresh adrenals from the sheep, finely divided and mixed with powdered sugar, or, better, the use of the active principle, adrenalin, supracapsulin, etc., 10 to 20 drops daily divided in five or six doses. Kirchheimer²¹³ has found large doses (10 to 24 minims) safe hypodermically in the collapse of pneumonia, diphtheria, and scarlet fever. Letulle, Lemoine, Grysez, and Dupuich^{213a} have found it of great value in the latter disease. Lesné, Gérard, and Francon^{213b} noted that the sudden death in erysipelas showed the characteristic symptoms of adrenal inhibition and obtained good results from the internal use of adrenalin and digitalis. The better plan, from my viewpoint, is to inject adrenalin with saline solution (at 108° F.) intravenously.

²⁰⁸ Hoddick: *Centralbl. f. Chir.*, Oct. 12, 1907.

²⁰⁹ Josué: *Loc. cit.*

²¹⁰ Netter: *Soc. Médicale des Hôpitaux*, May 7, 1909.

²¹¹ Marran and Darré: *Journal des praticiens*, May 15, 1909.

²¹² Moizard: *Revue de thérapeutique*, Jan. 1, 1910.

²¹³ Kirchheimer: *Münch. med. Woch.*, Dec. 20, 1910.

^{213a} Lemoine, Grysez, and Dupuich: *Bulletin médical*, Jan. 17, 1912.

^{213b} Lesné, Gérard, and Francon: *Presse médicale*, Nov. 15, 1911.

These measures are only indicated in emergency cases, however. In the average case the *glandulæ suprarenales siccae* of the U. S. P. administered by the mouth is fully as effective if a good preparation is obtained as soon as asthenia and low blood-pressure appear. The powder in 3-grain (0.2-Gm.) doses three times daily in capsules, gradually increased until 5 grains are given at each dose, usually suffices. When the cardiac adynamia disappears, a small dose of thyroid, the desiccated gland, also $\frac{1}{2}$ grain (0.03 Gm.) strychnine $\frac{1}{60}$ grain (0.001 Gm.) and Blaud's pill, 1 grain (0.06 Gm.) added to each capsule greatly hastens convalescence. The iron and the adrenal product serve jointly to build up the hæmoglobin molecule, a slow process when left to itself.

For our knowledge of the action of the use of pituitary extracts in infectious diseases we are mainly indebted to L. Rénon and Delille,²¹⁴ who began their use in 1907. In a recent work in which the observations of both observers are recorded, Delille,²¹⁵ referring to grave cases of typhoid fever, states that they showed "arterial hypotension, irregularity of the pulse (especially the grave forms), oliguria, insomnia; while convalescents showed asthenia, hypotension, or at least effort hypotension (Oddo and M. Achard), paroxysmal or continuous tachycardia"—all, we have seen, symptoms of hypoadrenia. They found $1\frac{1}{2}$ grains of pituitary extract (of both lobes), at noon daily, extremely efficient; it counteracted at once the depressed arterial tension, produced diuresis, relieved the insomnia, and greatly improved the general condition. Similar effects were observed in diphtheria and erysipelas. The use of the pituitary extract "vaporole," as described under the preceding heading, is also indicated in these cases. The results in pneumonia do not appear to me to warrant the use of any adrenal or pituitary preparations early in the case, the first few days of the disease, when the blood-pressure and the fever are high. They should be used *only when a low blood-pressure and other symptoms of hypoadrenia are present*. The results reported by Delille strengthen this opinion. In advanced tuberculosis no beneficial effect was observed.

²¹⁴ Rénon and Delille: *Bulletin de thérapeutique*, Feb. 8, 1907.

²¹⁵ Delille: "*L'Hypophyse et la Médication Hypophysaire*," 1909.

HYPERADRENIA.

Just as "hypoadrenia" has seemed to me to replace advantageously both "adrenal insufficiency" and "hypoadrenalism," so does "hyperadrenia" appear to convey a more exact meaning of excessive adrenal activity than "hyperadrenalism," which suggests the presence of habitual overactivity, and to be less cumbersome than the phrase "excessive secretory activity" and others habitually used.

To recall briefly the effects of large doses of adrenal extract, is all that is necessary in the present connection. Textbooks merely refer to the fact that it causes marked slowing of the heart, marked constriction of the blood-vessels, and a decided rise of blood-pressure; but we would not proceed far with these archaic limitations were we to attempt to explain with them the phenomena included under hyperadrenia. I shall, therefore, continue to have the interpretation of the phenomena witnessed upon the conception of adrenal functions I have advanced, viz., that the adrenals supply a secretion which becomes converted in the lungs into the oxygenizing albuminous constituent of the hæmoglobin molecule, and that as such it governs metabolism and nutrition, the action on the heart and blood-vessels being but an incidental result of this function. We have seen also that the adrenal secretion took part in the immunizing processes of the body at large. We shall now find that these functions account for those of hypoadrenia, as they did under the preceding heading.

Were we to identify a "functional" type, as I did in the opposite condition, hypoadrenia, we should find it necessary to include the many conditions in which overactivity of the adrenals takes an important part. When we recall, however, that, from my viewpoint, these organs play a leading rôle in all febrile affections, that an excess of adrenal secretion in the blood means hyperoxidation and hyperactivity of all organs, and that as a result we may have glycosuria, psychoses, pulmonary œdema, and many other symptoms, it will become apparent that no such a "functional" type could well be proposed without endowing the adrenals with a great part of the whole field of pathology. It was deemed far preferable, therefore, to treat

known diseases in the usual way and to illustrate the rôle played in their history by the adrenals. This has been carried out in the second volume, beginning with page 1389, reserving for the present chapter what disorders could strictly be associated with the adrenals *per se* or due essentially to an excess of adrenal tissue, as in the various forms of hypernephroma.

In point of frequency, subdivision of the subject is not difficult to establish, the first condition, treated below, being one which the general practitioner is liable to meet at any moment and continuously in the course of his everyday work.

ACUTE HYPERADRENIA AND ADRENAL HÆMORRHAGE.

By the term "acute hyperadrenia," I mean excessive functional activity of the adrenals or "hyperadrenalism," brought on by the presence in the blood of the system at large of any poison capable of exciting the adrenal center.

We have seen that various toxics, pneumobacillus cultures, diphtheria and other toxins, drugs, vegetable poisons, etc., caused, when injected experimentally, congestion of the adrenals, so marked in some instances as to provoke rupture of the congested vessels, or necrosis of the adrenal cellular elements compressed by them. To the confirmatory investigations already mentioned may be added those of Bernard and Bigart,²¹⁶ who studied the effects of arsenic, mercury, and lead, mainly in respect to the histological changes produced in the cellular elements of the adrenals, and who found that in the *less profound* intoxications there occur, instead of destructive lesions, the histological signs of *functional hyperactivity*. My own investigations have not only sustained this conclusion, but they have served to explain the manner in which this functional hyperactivity is brought about, viz., by excitation of the adrenal center, which, as already stated, I traced to the pituitary body.

As previously shown, we are dealing with the manifestation of an immunizing function in which the adrenals take part. Important to recall in the present connection, however, is that, when the intoxication becomes excessive, it may entail grave consequences. The intra-adrenal vascular channels, abnormally

²¹⁶ Bernard and Bigart: Jour. de physiol. et de pathol. générales, No. 6, p. 1014, 1902.

engorged through the marked back pressure induced by the high blood-pressure caused by the excess of adrenal secretion, are exposed to rupture. This hyperactivity of the adrenals (acting in conjunction with the thyroid) constitutes the phenomenon, so far unexplained by pathologists, of *fever*, while the excessive activity which exposes the adrenal vessels to rupture coincides with that of *hyperpyrexia* in these acute infections. In other words, the hyperadrenia which occurs in the course of acute febrile infections or intoxications is the expression of an immunizing process, but this assumes dangerous proportions and involves the danger of fatal adrenal hæmorrhage when excessive, *i.e.*, when the immunizing process exceeds certain limits.

Acute hyperadrenia, therefore, is that condition of the adrenals which precedes adrenal hæmorrhage in any febrile infection or intoxication, and the danger-signal of which is hyperpyrexia.

This does not mean that febrile infections and intoxications alone expose the adrenals to hæmorrhage; we have seen that many poisons and drugs even may do so by raising or depressing unduly the blood-pressure through a direct action on the vaso-motor center. This process has been reviewed in sufficient detail. We shall now deal only with diseases due to toxins and endogenous poisons, toxic wastes, etc., that are capable of enhancing the adrenal functions to awaken a defensive process and, as a complication, adrenal hæmorrhage, and treat both conditions jointly, the better to emphasize their close clinical relationship.

Adrenal hæmorrhage first described as a disease by Rayer²¹⁷ early last century, and cases of which have been reported by Addison, is of common occurrence pathologically. Besides the evidence previously submitted illustrating the frequency with which this morbid process is observed may be mentioned the fact that, in 150 random autopsies, Loeper and Oppenheim²¹⁸ found, aside from instances of simple congestion, which were very numerous, 5 true hæmorrhages visible to the naked eye and 8 discernible microscopically. The proportion was much greater when infectious diseases had been the cause of death; and they hold that a large number of similar lesions are masked by

²¹⁷ Rayer: *L'Expérience*, May 10 and Nov. 10, 1837.

²¹⁸ Loeper and Oppenheim: *Loc. cit.*, p. 722.

cadaveric changes: adrenal congestion and necrosis being frequently present together. The newborn showed a special predisposition to this complication, the proportion of 250 autopsies being 45 per cent. That we are dealing with a frequent, though generally overlooked, cause of death, is evident.

While disorders of respiration predominate as cause in the newborn, infections do so in children and adolescents. Then come, in order, and, apparently, as the most frequent causes in adults: pulmonary disorders, especially tuberculosis and pneumonia; nervous diseases, particularly meningitis and epilepsy; chronic renal diseases, arteriosclerosis, cancer, abscess, burns, and general paralysis of the insane. Purpura is often regarded as a cause, but this should be considered, from my viewpoint, as a precursor or danger-signal of adrenal hæmorrhage, though the purpuric spots, which are in reality cutaneous hæmorrhages, persist after the adrenal hæmorrhage has occurred.

From the facts submitted below, I would define adrenal hæmorrhage as *an extravasation of blood into one or both adrenals due to rupture of some of their blood-vessels when, as a result of high blood-pressure throughout the body from any cause: torins, toxic wastes, etc., these vessels are subjected to centrifugal pressure exceeding the resistance of their walls.*

PATHOGENESIS AND SYMPTOMATOLOGY.—Although adrenal hæmorrhage is due to the rupture of the vascular elements when the congestion of hyperadrenia exceeds safe limits in all cases, the pathogenesis of adrenal hæmorrhage varies considerably in its general lines according to the age at which it occurs. This applies also, to a limited extent, to the symptomatology. It becomes necessary therefore to divide the cases into three general groups, viz.: (1) the newborn, *i.e.*, during the first days of life; (2) children, up to puberty, and (3) adults, *i.e.*, beyond puberty.

Adrenal Hæmorrhage in the Newborn.—In these, adrenal hæmorrhage occurs within a few moments or days after birth. In a small proportion of cases, death ensues, without premonitory symptoms, shortly after birth. Delay or injuries in the course of delivery or interference therewith by malpositions, or any of the causes which are apt to render artificial respiration necessary, predispose to it. In another class of cases the infant,

having shown perhaps some slight difficulty in breathing or a tendency toward cyanosis, suddenly ceases to nurse; reddish-purple or bright-red spots of purpura appear on the face, neck, buttocks, or extremities; a convulsion follows, with death in its wake. Or again, patches of purpura appear, the infant refuses the breast and becomes somnolent, then suffers from colic, diarrhœa, vomiting, and fever and becomes rapidly emaciated. Convulsions usually precede death.

All such cases are due, from my viewpoint, to the inadequacy of the defensive resources of the infant, *i.e.*, its inability to counteract an endogenous toxæmia. As previously stated and as will be emphasized later, the adrenal system (consisting of the adrenals, thyroid, and pituitary, and to which I attribute a leading rôle in all immunizing functions) is not sufficiently developed in the nursling to protect it adequately against toxics of various kinds; the maternal milk provides the immunizing constituents derived from her own adrenals and thyroid to compensate for this function. My opinion has been recently sustained by Fassin, Stepanoff, and Marbé,²¹⁹ and also by Concetti²²⁰ as to the influence of the thyroid in the process, while the immunizing property of maternal milk as a compensating factor for the deficiency of the suckling has been sustained by Ehrlich and Brieger, Abraham Jacobi, Welch, and others. Now, at birth, any condition which diminishes materially the immunizing activity of the maternal milk, or which, in the nursling, interferes with the utilization of the maternal immunizing bodies, such as a deficient intake of oxygen, asphyxia, hypocatabolism, etc., correspondingly impairs the power of the infant to break down its waste products, thus allowing these poisons to accumulate in the blood. Precisely as they are known to do in epilepsy, eclampsia, and other convulsive disorders, these endogenous intermediate wastes cause a violent elevation of the blood-pressure,—sufficient to cause rupture of the delicate but rich vascular network of the adrenal medulla, localized capillary hæmorrhages in the skin, *i.e.*, the purpura, melæna, hæmoptysis, epistaxis, and other forms of hæmorrhage witnessed. Vomiting and diarrhœa occur as results of the marked congestion in the

²¹⁹ Léopold Lévi and de Rothschild: *Physio-pathologie du corps thyroïde*, p. 20, Paris, 1911.

²²⁰ Concetti: *Revue d'hygiène et médecine infantiles*, No. 3, 1910.

alimentary canal, while convulsions are produced by a corresponding hyperæmia of the cerebrospinal axis.

This accounts for the fact that these cases cannot be traced to infection or ascribed to the presence of any pathogenic organism (though we shall see presently that infection often causes adrenal hæmorrhage in older children), and also for the frequency of adrenal hæmorrhage the first few days after birth, especially where there is any indication of deficient respiration, or, as in the cases witnessed by Northrup, an incomplete septum lucidum.

The cortex is sometimes greatly distended by the hæmorrhage, and the friable medulla of the organ completely disorganized and replaced by a black blood-clot.

Adrenal Hæmorrhage in Children.—This is due to an entirely different class of causes, though the morbid effects and the symptomatology are very similar. Here again death occurs sometimes more or less suddenly in the course of the causative disorder, or, in fact, sometimes before its exact nature has been determined, though in most cases the lethal collapse is preceded by purpuric spots. If the causative disorder be an exanthema, varicella, for example, the eruption may itself show a change, each patch assuming a bluish or cyanotic tinge, soon followed by collapse. In most cases, however, there occurs two, three, or more of the following symptoms: vomiting, fever, marked prostration, a more or less extensive petechia or a purplish purpuric eruption, dyspnœa or at least rapid respiration, diarrhœa with perhaps abdominal pain radiating into the loins, due to pressure of the dilated adrenals upon the adjoining sympathetic plexuses, and convulsions, cyanosis, and collapse—forming an incomplete and variable syndrome which is characterized by a feature common to all—its rapid termination in death, *i.e.*, within a period varying from a few to forty-eight hours.

That a toxæmia underlies all cases, as in the newborn, is also evident: but its source is entirely different. Adrenal apoplexy has been met in the course of several of the exanthemata, varicella, variola in the unvaccinated, diphtheria, and scarlatina especially; during convulsions or as a complication of abscesses, pyæmia, septicæmia, hydatid cysts, bronchopneumonia, ptomaine poisoning, or after extensive burns and severe injuries.

It has also been attributed to the staphylococcus pyogenes aureus and albus (Riesman, Dudgeon), the streptococcus (Drysdale), the pneumococcus and bacillus coli communis (Rivière), the meningococcus (Candler), and to other micro-organisms. On the whole, it may be due to many morbid conditions; but the one striking feature of all these causative disorders is that they are all of such a nature (febrile diseases, convulsions, etc.) as to provoke a rise of blood-pressure. Just as we have seen the latter to be the cause of adrenal hæmorrhage in the newborn, so is it in children. Dudgeon²¹ states that "any disease which is known to produce stagnation of the blood in the veins or a marked increase of the blood-pressure may be associated with adrenal hæmorrhage"; I would say instead that such a condition of the circulation tends to *produce* the latter as a complication.

Here again we are likely to find one or both glands more or less filled with a black coagulum with, occasionally, extravasation, or here and there hæmorrhages into the medulla or under the cortex, raising the corresponding portion of the latter.

Adrenal Hæmorrhage in Adults.—Adrenal hæmorrhage in adults is now thought to be rare, but this is probably due to the fact that it is seldom recognized. Although sudden death may occur without premonitory symptoms of the hæmorrhage in the adrenals, there is usually more or less sudden pain—sometimes excruciating—in the abdomen, radiating toward the back, under the costal margin; tympanites, vomiting, prostration, great weakness, copious and stubborn diarrhœa. Hæmorrhagic purpura and cutaneous hæmorrhages may also appear, but purpura is much less common than in children; anæmia, with a yellowish tinge of the skin ranging from sepia or light brown to the bronzing of Addison's disease in which adrenal apoplexy is not uncommonly observed. When it occurs in the midst of a convulsion, during an epileptic fit, for example, the patient may either die on the spot or show, on recovery, unusual asthenia, with, perhaps, uncontrollable diarrhœa. Gradually the pulse and respiration become weak, more or less cyanosis appears, followed by coma and death. Unusual physical exertion has also been known to cause adrenal apoplexy and sudden death. Acute

²¹ Dudgeon: Amer. Jour. Med. Sci., Jan., 1904.

nephritis is an occasional cause, death occurring suddenly with, perhaps, symptoms of pulmonary œdema.

The prevailing feature of adrenal hæmorrhage in adults is the presence of lesions in the adrenals themselves which cause these organs to yield with abnormal facility when a general rise of blood-pressure is brought on by any one of many causes. In adrenal apoplexy occurring in the course of Addison's disease, for example, the tissue-wastes which accumulate in the blood as a result of the diminished antitoxic power of the diseased adrenals excite, we have seen, the vasomotor center, and increase in proportion the vascular tension and blood-pressure. In the course of an epileptic fit the same exciting cause prevails, since, as is well known, the vascular tension is always marked. Over-exertion may produce adrenal hæmorrhage through the same mechanism, owing to the accumulation in the blood of an excess of tissue-wastes. Acute nephritis also produces it by raising the vascular tension; in a case of this kind reported by Loederich²²² this feature of the case is specifically noted. The production of adrenal apoplexy in Addison's disease by injections of adrenalin has also been reported in 2 cases (Boinet)—owing obviously to the rise of blood-pressure which this agent produces. Common to adults also is the form due to arteriosclerosis, the adrenal intrinsic arteries yielding here, as they do in the brain, owing to atheromatous degeneration, when from any cause the blood-pressure exceeds certain limits.

On the whole, it is apparent that adrenal hæmorrhage presents many features in common with cerebral hæmorrhage in which the gradually weakened vessel, particularly where, in the case of adults, arteriosclerosis prevails, can no longer sustain anything beyond the minimum blood-pressure.

Many auxiliary factors tend greatly, however, to impair the resistance of the adrenal vessels and tissues. As shown by Claude Bernard, hyperæmia is a cardinal feature of function. The adrenal vessels are already congested and under stress, therefore, when they are submitted to the excessive centrifugal tension which a marked rise of blood-pressure entails. Again, in the light of modern researches, and as will be demonstrated later in this work, the blood contains, during the febrile stage

²²² Loederich: *Le Bulletin Médical*, July 8. 1908.

of infections and intoxications, bactericidal and antitoxic bodies to which autolysis, under certain conditions, is ascribed. That the rich vascular elements of the adrenals and even the delicate adrenal medulla are probably subjected to such a process and thus rendered more vulnerable, in the course of acute febrile infections, is suggested by the areas of necrosis in these structures which many autopsies reveal. I must state, however, that I am not inclined to accept the conclusion that these necrotic areas are due to post-mortem changes, and that I regard them as due more to a process of autodigestion similar to that known to exist in the gastric mucosa. This subject cannot, however, be considered here.

DIAGNOSIS.—The most important feature in this connection is to differentiate clearly the prehæmorrhagic from the post-hæmorrhagic phenomena. Careful attention in this particular makes it possible to save life, since the prehæmorrhagic symptoms include several which may be regarded as danger-signals to the effect that the blood-pressure is dangerously high, and that the adrenals are threatened.

In the *infant*, imperfect respiration following delayed delivery, purpura with or without fever points clearly to impending hæmorrhage: The course of events then, if no prophylactic measures are taken, will be the appearance in a few hours of the posthæmorrhagic state: abdominal pain, diarrhœa, vomiting, soon followed by a gradual decline of the temperature, coldness of the extremities with convulsions or cardiac collapse as terminal phenomena.

In the *child*, the presence of fever and high blood-pressure in the course of any infection entail the possibility of adrenal hæmorrhage, especially when any eruption that may be present tends to spread, or where purpuric spots are present. Here again, if not avoided by appropriate treatment, the posthæmorrhagic phenomena appear, likewise ending in death in a few hours.

In the *adult*, the great variety of disorders which, besides the acute infections, adrenal hæmorrhage may suddenly complicate would seem to preclude the possibility of preventive measures, but if it is remembered that the adrenals are exposed to hæmorrhage *whenever the blood-pressure is high from any cause*, as suggested by venous engorgement, venous pulse, facial

congestion, and a hard pulse, with the sphygmomanometer as control, the danger can as readily be forestalled as in the young. We must also, in the adult, take into account the possibility of adrenal hæmorrhage in all asthenic diseases of the adrenals themselves, particularly the tubercular lesions of Addison's disease in which death frequently occurs suddenly. In all of these, the symptoms of hypoadrenia are present, particularly muscular asthenia, emaciation, hypothermia, hypotonia or low blood-pressure, and feeble pulse.

The onset of adrenal hæmorrhage in adults is characteristic in its abruptness, the severity of the abdominal pain, and the rapidity with which it is followed by general collapse. The incoercible vomiting and diarrhœa (either one or both), the hypothermia, the cold sweats, the feeble pulse and heart action, the coma or convulsions with sudden death in their trail are unmistakable signs of sudden arrest of the adrenal functions.

The absence of all reference to adrenal hæmorrhage in textbooks has caused it to be mistaken for arsenic poisoning and other intoxications, cholera morbus, appendicitis, cerebral apoplexy, and other acute disorders.

PROGNOSIS.—As will be shown presently, adrenal hæmorrhage may be followed by the development of hæmatomata in the adrenals proper, proof evident that not all cases are necessarily fatal, particularly small hæmorrhages located in the depths of the organ. It is probable, therefore, that when the likelihood of this complication will be borne in mind by the practitioner when treating any one of its many causes, and its main cause, excessive vascular tension, generally recognized and counteracted, its present high mortality will be greatly reduced.

TREATMENT.—The multiplicity of pathogenic factors and of symptoms, sufficient to have suggested many clinical types to various authors, has, so far, prevented the elaboration of any treatment calculated to prevent or arrest adrenal hæmorrhage and its rapidly fatal course. With excessive blood-pressure as the direct cause of the disruptive congestion of the adrenal vessels, however, a general line of treatment calculated to relieve it obviously imposes itself.

In a threatened case, antipyrin or other coal-tar products suggest themselves; but their use cannot but prove pernicious,

owing to the primary action on the vasomotor center. By exciting this center and raising the blood-pressure they increase the likelihood of adrenal hæmorrhage, a fact which probably accounts for the many instances of fatal collapse observed under their use in acute febrile diseases. The physiological saline solution offers, on the other hand, all desirable qualities. It does not, as argued theoretically by some authors, increase the vascular tension, even if injected intravenously; as shown by the experiments of Sollmann,²²³ Briggs,²²⁴ and others, any excess of fluid leaves the vessels at once. By reducing the viscosity of the blood, saline solution tends to relax the blood-vessels; by increasing its osmotic properties, it facilitates greatly the penetration of the plasma into the lymphatic channels, thus further reducing the vascular tension. The bactericidal and antitoxic properties of the blood are not reduced in the least by this procedure; there is considerable evidence available to show, in fact, that they are enhanced (see p. 1367). Saline solution, therefore, should be used intravenously in emergency cases; subcutaneously in threatening cases, and per rectum in all cases in which there is any likelihood whatever that adrenal hæmorrhage might occur. If employed from the onset of all infections, as I suggested in 1903, the blood-pressure would probably never be raised sufficiently to endanger the adrenals.

As to drugs, we have several at our disposal which lower the blood-pressure. In emergency cases, nitrite of amyl by inhalation, with nitroglycerin (or in children the sweet spirit of niter) to sustain the effect, appears indicated. Chloral hydrate has been used advantageously by J. C. Wilson in certain exanthemata, to subdue the cutaneous discomfort and as a sedative; as it is also a vasomotor depressor, it might also serve advantageously in all but infants in whom the respiratory mechanism is defective. Veratrum viride suggests itself as another useful agent of this class. Of all measures, however, the saline solution is much to be preferred.

When the hæmorrhage has occurred, the lethal phenomena are of such short duration in most cases as to have suggested, we have seen, the term "adrenal apoplexy." In a fair proportion

²²³ Sollmann: *Archiv f. exp. Path. u. Pharm.*, Bd. xlvI, S. 1, 1901.

²²⁴ Briggs: *Johns Hopkins Hosp. Bull.*, Feb., 1903.

of cases, however, the hæmorrhage causes sudden hypoadrenia. The treatment of this condition is that indicated in the emergency cases of terminal hypoadrenia (see page 113). If the hæmorrhage has not been too extensive the chances of recovery will be greatly increased by the use of adrenal or pituitary preparations, the latter owing its properties, in my opinion, to the adrenal chromaffin substance the pituitary contains.

ADRENAL HÆMATOMA.

(Adrenal Hæmorrhagic Pseudocyst.)

Adrenal hæmatoma, which usually develops in but one adrenal, occurs as a complication of the condition just reviewed. It becomes a source of fatal adrenal hæmorrhage when the cyst breaks and empties its contents into the abdominal cavity. It indicates that the form previously described is not always fatal, but also that the lesions left behind may serve as the initial lesion of another grave disorder. Especially does this apply when but one adrenal is the seat of hæmorrhage. Its original causes, when these are traceable, are the same as those of the acute form: acute intoxications, especially diphtheria, typhoid fever, burns, osteomyelitis, hepatic abscess and tuberculosis, atheroma of the adrenal arteries, thrombosis of the adrenal veins, traumatisms, etc.

PATHOGENESIS AND SYMPTOMATOLOGY.—While older investigators, including Klebs, Virchow, and Heuschen, considered these growths as retention cysts similar to those formed in the thyroid, and thus termed them “struma adrenalis,” the prevailing view at the present time is that a small hæmatoma or an acute congestive process initiates the growth. As the latter increases in size, the adrenal structure is gradually destroyed and the contents is no longer—unless a recent hæmorrhage has occurred—merely blood, but a more or less fluid magma of detritus, broken-down blood- and tissue- cells, flakes of fibrin, cholesterin crystals, etc., which may be dirty yellow, greenish, or brownish in color. Microscopically the walls of the cyst, which vary from $\frac{1}{16}$ to $\frac{1}{8}$ inch in thickness, are composed of fibrous tissue; the inner aspect shows shreds or remnants of the adrenal cortex. Certain thickened portions of the capsule and what

semiorganized clots the cyst may contain may be found to contain small cysts and chalky deposits. These growths sometimes become very large—as large as an adult head in a case of Chiari's—and contain several pints of blood or liquefied blood and tissue elements.

The symptomatology of adrenal hæmatoma introduces but little, if anything, of the symptom-complex of adrenal insufficiency (hypoadrenia) or overactivity (hyperadrenia), since the functions of the organs are not affected materially—otherwise than by pressure in some instances—owing to the ample margin (eleven times the actual needs of adrenal tissue) left undisturbed. Adrenal hæmatoma may, in fact, give rise to no symptom other perhaps than a sensation of weight, until quite large, when pain supervenes. This is at first indefinite, though most marked in the region of the tumor, in the right or left loin, or in the upper portion of the abdomen and loin. The neuralgia-like pain due to pressure upon the adjoining sympathetic plexuses becomes increasingly severe, and radiates in various directions, especially toward the hip and thigh of the corresponding side, and is subject to exacerbations, which may be very severe, especially after meals. Epigastric pain and vomiting (the latter of which affords relief) occur in some cases, especially during these exacerbations of suffering.

The tumor may manifest itself, at first, merely by enlargement of the abdomen. The bulging then becomes more clearly defined on one side or the other (this variety of growth being almost invariably unilateral) under the lower ribs, which may be pushed outward if the growth is sufficiently large, or below their free border, *i.e.*, between them and the superior spine of the ilium. If the tumor, which grows downward and forward, is sufficiently below the ribs to be palpated, it is usually found globular, or oval, smooth and tense, though elastic, to the touch. Fluctuation may also be elicited. In some cases it is immovable under palpation, though it may, at first, follow the respiratory movements. Nor can it be grasped as is sometimes possible in renal tumors; if small the tumor is movable either upward or downward, but this mobility gradually decreases as the tumor develops. The growth is sometimes sensitive under pressure.

At first, several years perhaps, the patient may appear

normal in every other respect, be well nourished, ruddy, etc. With comparative suddenness, however, he begins to fail, losing flesh rapidly, all the other symptoms mentioned, to which dyspnœa and a sense of constriction about the chest is added, becoming more severe. If the cyst does not rupture, polyuria, hæmaturia, and even slight bronzing may appear. It is probable, however, that this train of phenomena is witnessed only in a very small proportion of cases, rupture and hæmorrhage, constituting the "adrenal hæmorrhage" in adults treated under the preceding heading, being the outcome in practically every instance. Here, however, the rupture is external, giving rise to peritoneal manifestations—if these have sufficient time to develop at all.

DIAGNOSIS.—The symptomatology of adrenal cyst apart from the location of the tumor does not present, as just shown, very characteristic features. The location of the pain sometimes suggests intercostal neuralgia; but, inasmuch as pain occurs only when the growth is large, percussion and palpation will reveal the presence of a tumor. In neuralgia the pain is also apt to be localized, thus distinguishing it from the radiating pain of adrenal cyst. The sudden onset of severe pain may be taken for acute pancreatitis. The location of pain and tenderness in the upper left abdominal quadrant, the subnormal temperature, and the early lethal trend—death occurring sometimes within three days—clearly point to the latter disease. Pancreatic cyst is also differentiated by its location and its association with glycosuria, stearrhœa, and imperfect digestion of fats and albuminoids. Hydatid cyst of the liver, another source of confusion, is attended by the presence of biliary pigments in the urine, the appearance of cysts in the stools and vomited matter, and with obstruction phenomena. Cancer of the spleen may be recognized by the more nodular outline of the growth and the cachectic phenomena. Hydatid cyst of the spleen is usually associated with hydatid cysts elsewhere and may be accompanied by the presence of hooklets in the excretions. Puncture of the growth should be carefully avoided when there is any suspicion whatever that an adrenal blood-cyst is present. Renal cysts are more easily palpated bimanually, and are usually freely movable.

The sudden appearance of symptoms of severe internal

hæmorrhage (the adrenal hæmorrhagic cyst having ruptured into the peritoneal cavity or the subperitoneal cellular tissue), *i.e.*, the acute abdominal pain and other phenomena of collapse, etc., of adrenal hæmorrhage with death within a few hours or days, may first reveal the existence of adrenal hamatoma; but in most cases it develops sufficiently to produce the pressure symptoms just described.

PROGNOSIS.—The fact that adrenal hæmorrhage is practically always unilateral, and that the loss of one adrenal does not compromise life, as does removal of both organs, makes it possible to remove the growth with safety. The frequent instances of severe collapse and shock that have followed these operations suggest that the operative prognosis cannot but be improved by resorting to those surgical procedures which will entail the least possible handling of the intraperitoneal organs and of the sympathetic ganglia, all of which are well known to produce shock readily by reflex action.

TREATMENT.—The cyst may be removed through either an abdominal or lumbar incision. In accord with M'Cosh's advice, which a review of the operative results recorded fully sustains, preference should be given to the lumbar incision. The approach is more direct; it avoids the handling of the intraperitoneal organs, which must necessarily take place if the tumor be reached through the abdominal incision, and it affords the most direct route for drainage. In the average case, an oblique incision from behind downward and forward below the last rib, which has been found most convenient for extirpation of the kidney and ureter, is as applicable here. If much space is needed it is safer to remove the last rib than, as some European surgeons have advised, to resort to the abdominal incision, which, as previously stated, entails considerable shock. The tumor is sometimes found so firmly adherent to the kidney that removal of this organ becomes necessary.

HYPERNEPHROMA.

This name has been given to tumors formerly considered as lipomata, adenomata, or myxomata, but shown by Grawitz, in 1883, to be developed from adrenal tissue, either within the adrenals themselves or in the kidneys, the walls of blood-vessels,

or other structures in which "adrenal rests" (fragments of misplaced adrenal tissue) or "aberrant adrenals" occur.

From my viewpoint, these so-called "adrenal rests"—found in 90 per cent. of all autopsies by Bayard Holmes, at least once a week by Grawitz in his autopsies, etc.—are not misplaced fragments of adrenal tissue; they belong normally to the kidney and many other organs, notwithstanding their histological characters. I have advanced the view²²⁵ that what has been termed the internal secretion of the kidney is a product which differs in no way from that of the adrenals, and²²⁶ that the kidney and the adrenals were governed by the same nervous structures, being thus closely linked functionally. Under the influence of centric impulses the so-called adrenal rests and the adrenals are both caused to increase their secretory activity and to enhance the intrinsic metabolism of the tissues they supply. On the whole, I regard the "adrenal rests" as local aggregates of the chromaffin substance found in all sympathetic structures by Kohn, Wiesel,²²⁷ and others.

Hypernephromas are relatively common in the kidney, constituting, as shown by Albarran and Joubert, 17 per cent. of all renal tumors; they are much less frequently found in the adrenals proper or in other organs, such as the uterus, ovary, the broad ligament, etc. Microscopically, they present the typical characters of the adrenal cortex and closely, as a rule, invest vascular channels. These vessels and adjacent tissues usually contain a colloid material similar to that found in the thyroid, or secreted by the adrenals. They are benign at first and become troublesome—sometimes after many years—mainly on account of their size, which sometimes reaches that of a child's head, but the pressure they exert on surrounding structures, their tendency, even when benign, to metastasize in the lungs, bones, brain, give them their malignancy.

PATHOGENESIS AND SYMPTOMATOLOGY.—Before the local symptoms of the tumor appear—when any are clearly discernible—hypernephroma evokes phenomena which are diametrically opposed to those of Addison's disease, and which correspond

²²⁵ Sajous: *Monthly Cyclopædia*, June and July, 1909.

²²⁶ See p. 259, this volume.

²²⁷ Wiesel: *International Clinics*, vol. II, 15th series, 1905.

with increased nutrition and stimulation of growth such as that produced by thyroid preparations in cretinism.

The symptomatology varies considerably in different cases and suggests that several types exist which our present knowledge does not enable us to discriminate. Some of these exhibit such malignancy that they have been grouped in a separate class. Beginning with hypernephromas of the adrenals proper, we may have:—

Malignant Hypernephroma of the Adrenals.—This growth occurs as a rule between the first and eighth year, especially in girls of the latter age, and causes premature development, so marked in some instances that the child appears, as to size and development, twice or three times its true age. Owen Richards²²⁸ reported a case in a girl of 7 years, who was as tall as a person at 20. The face, genitalia and pubis, and sometimes the whole body are covered with an abundant growth of hair, the external genitalia being as fully developed as in the adult. The body is obese, the appetite and thirst excessive although gastric disorders, including stubborn vomiting, are common. The skin may be swarthy or dark-hued as in a brunette, or coppery. The voice is sometimes harsh and deep. Such children are usually cross and sullen, unlike obese children in whom the obesity is due to deficient fat catabolism. These primary growths of the adrenals, which are usually observed in girls, are of slow development, and years usually elapse before metastasis and pressure phenomena—those which give the growth its malignancy—appear.

The abnormal growth of the child may suggest gigantism or acromegaly due to some disorder of the pituitary body, but the characteristic growth of the extremities, the absence of obesity in these disorders do not occur in hypernephroma.

To explain the abnormal growth, we need not go beyond my own view that the adrenal secretion underlying general oxidation, metabolism and nutrition, excessive functional activity of the adrenals engenders excessive nutrition and overgrowth. But how account for the malignancy of this form of growth? To answer this would bring us within the domain of pure

²²⁸ Richards: Guy's Hospital Reports, vol. lix, pp. 207-332.

speculation. It is preferable to limit ourselves to clinical facts, pending future developments.

Infants and young children are also subject to a form of primary malignant tumor of the adrenals, described by Hutchison, in which, even before the neoplasm, which grows with great rapidity, can be felt in the renal region, there appears a spontaneous—sometimes traumatic—ecchymosis of one or both eyelids, soon followed by (usually unilateral) exophthalmos and metastasis in the skull, and often in other bones, especially the ribs. The preauricular lymph-nodes and those behind the angle of the jaw are enlarged, and the whole temporal region eventually becomes the seat of a malignant growth. Pain in this location and optic neuritis with amblyopia may complicate the case. Death occurs early from anemia and cachexia. Of the 14 examples reported, 13 were due to sarcoma or lymphosarcoma of the adrenals.

DIAGNOSIS.—Tumor of the orbit in infants and young children should, as emphasized by Tileston and Wolbach,²²⁹ arouse the suspicion of metastases from an adrenal growth. If an abdominal tumor be found it is almost certainly of adrenal origin, and this would be still further corroborated by enlargement of the preauricular glands, which renders the diagnosis of sarcoma of the orbit unlikely. Chloroma presents almost identical growths, being associated with tumors of the orbit in two-thirds of the cases, with exophthalmos usually as the first symptom, but this may be excluded in the absence of leukæmic changes in the blood. Myeloma may cause bony growths about the skull, but is exceedingly rare in childhood; the presence of the Bence-Jones body in the urine would render the diagnosis of myeloma certain, while its absence is not conclusive. Abdominal tumor associated with precocious maturity is practically certain to be of adrenal origin, if tumors of the ovaries or a retained testis can be excluded. Garrow and Kennan^{229a} observed a case in which there was a solitary metastasis in the spinal cord.

Hypernephroma of the Kidney.—It is to renal growths developed from the so-called “adrenal rests” that Grawitz, in 1883, gave the name “hypernephroma.” They occur not only more frequently in the kidneys than elsewhere in the body, but

²²⁹ Tileston and Wolbach: Amer. Jour. Med. Sci., June, 1908.

^{229a} Garrow and Keenan: Med. Record, Jan. 17, 1912.

constitute a large proportion of all renal tumors, *i.e.*, 17 per cent.

Hæmaturia is often the first and the most frequently observed symptom of renal hypernephroma, having been noted in 90 per cent. of all cases. The hæmorrhages are usually severe and occur intermittently, weeks and even months elapsing between them. Worm-like clots—thus shaped during their passage through the ureters—are often passed. During the intervals the urine is either clear or it may contain red corpuscles. The hæmaturia is increased by exercise and by manipulation of the region overlying the growths if the latter is sufficiently large to be felt. It may be the only symptom of the growth or precede the detection of the latter by palpation as much as ten years. As a rule, however, the tumor (which occurs in 80 per cent. of all cases) is sufficiently large to be detected much earlier, and sometimes immediately after an attack of hæmaturia. It is located in the loin, often on the right side and two or three finger-breadths below the costal margin. It is at first small—about half the size of a walnut—and is movable in about one-half of the cases. As a rule, palpation causes no pain at first, though it may prove tender when directly pressed upon.

Dull pain in the lumbar region suggesting lumbago may be the initial symptom. This pain gradually increases and, after being centered in the region of the growth, with a sensation of weight, increasingly radiates in various directions, the back, the abdomen, and the testicles. It may come on suddenly and last three or four hours, then be followed by hæmaturia and frequent urination followed by a period of rest during which the urine is slightly albuminous. The urine sometimes contains a few casts, oxalate of lime, and a few corpuscles. During this period of rest a certain stiffness may be experienced on the side of the tumor. Varicocele is frequently observed in these cases, on the same side as the focus of pain; it may develop simultaneous with the latter and disappear when the patient assumes the recumbent position.

While periodical hæmaturia, a tumor and pain in the locations mentioned are typical signs of renal hypernephroma, other phenomena may appear gradually as the morbid process advances. Most important among these are the metastases, which occa-

sionally occur as first signs of the disease. This is especially the case in bone metastasis, which may appear in the vertebræ, the ribs and other long bones, the skull, scapula, etc., *i.e.*, practically any portion of the skeleton. Metastasis may also occur in various viscera, particularly the lungs, the consolidation in the latter suggesting the corresponding stage of phthisis.

The arteries may be thickened and show clearly defined signs of arteriosclerosis, quite in contrast sometimes with the relative youth of the patient, and the blood-pressure be quite high. The skin is not bronzed in these cases, but yellowish and, sometimes, swarthy or smoky, this being replaced by pallor when the end is near. The temperature may be raised, but this rarely exceeds 1° or 2° F.

An important feature in this connection is that bronzing is a characteristic of *insufficiency* of the adrenals, as in Addison's disease, whether due to degeneration, tuberculosis or malignant tumor of these organs or of their nerve supply. In hypernephroma, on the contrary, we have an addition of adrenal substance to the circulation through the secretory activity of the adrenal rests, as shown by the familiar results of adrenal over-activity enumerated—high blood-pressure and arteriosclerosis. The icterus or swarthiness here is due, from my viewpoint, to the continuously high blood-pressure which causes the cutaneous capillaries to become hyperæmic and to expose an increased quantity of the adrenal principle—the component of melanin (we have seen in the early portion of this chapter that melanin is the adrenal principle) to oxidation. The stage of bronzing is not reached, because the pigment is not deposited in the cutaneous tissues, as it is in Addison's disease, but merely supplied to them in excess.

The duration of the disease varies from fifteen weeks to eight years. The patient gradually loses flesh and grows weaker, all the symptoms become aggravated, hæmaturia becoming prominent and causing marked secondary anæmia; moderate œdema of the lower limbs may appear mainly as a result of pressure on some large venous trunk, and delirium sometimes precedes the terminal coma.

DIAGNOSIS.—The pain in the region of the affected kidney, the hæmaturia accompanied by frequent urination, and the local-

ized tumor are the chief diagnostic points among those previously enumerated, but other features may serve to facilitate the diagnosis. Gellé pointed out that fragments of the tumor, which is very friable and often dissociated during hæmorrhages, could be found in the clots passed with the urine. The cells preserve their characters and staining properties. As to diagnosis of the tumor itself after removal, Croftan found (1) that a watery extract of fresh hypernephroma, in keeping with adrenalin and adrenal extracts, provoked glycosuria when injected in the rabbit; (2) that a pure starch solution to which the watery extract of hypernephroma was added contained an appreciable quantity of dextrose, and (3) that the watery extract also possesses the power to decolorize an iodine starch solution. These simple tests make it possible to differentiate hypernephromata from other tumors of the kidney. This is important, since the post-operative prognosis of hypernephroma is much more favorable than that of any other malignant tumor of the kidney. A high blood-pressure tends greatly to insure the diagnosis.

Various disorders may be simulated by hypernephroma, prominent among which is urinary calculus. In this connection the pain is coincident with the hæmorrhage, while in hypernephroma the pain continues after the latter, though greatly relieved. The vermicular and cylindrical shape of the clots in hypernephroma is also suggestive. Cystoscopic examination at this time often reveals these clots projecting from the ureter of the diseased kidney, whose tumor can also, in some instances, be discerned under X-ray examination. Pregnancy is sometimes suggested when the growth projects *anteriorly*, especially in view of the fact that amenorrhœa sometimes precedes the abdominal enlargement.

Hypernephroma may be mistaken for enlarged spleen. The latter is usually nearer the surface and its mobility on inspiration more marked. It is located on the left side, whereas hypernephroma, in most instances, occurs on the right side. Catheterization of the ureters may serve to indicate, between the periods of hæmaturia, which of the two kidneys is most impaired functionally. The blood count affords little if any information, any diminution of red corpuscles—sometimes to an extreme degree—being readily accounted for by hæmaturia.

Moderate leucocytosis occurs in some cases, but not with sufficient frequency to give this sign any diagnostic importance.

In some cases the symptoms and physical signs other than hæmaturia afford but little help to establish the identity of the tumor, either anteriorly or posteriorly. In that case, the absence of pregnancy being clearly established, an exploratory incision followed immediately, if hypernephroma be present, by its radical removal, is indicated.

PATHOLOGY.—Hypernephroma is usually located in the upper pole of the kidney, immediately, therefore, under the adrenals. When found early in life at autopsies it may be no larger than a lentil or even smaller, but it may attain the size of a child's head, growing outwardly or, in some cases, inwardly at the expense of the renal tissues. These growths reproduce more or less perfectly the adrenal tissue, the smaller growths being made up, as a rule, of the cortex, and the larger of both the cortical and the medullary substance. They are firm when small, but when they attain a certain size their tendency is to become lobulated, the projecting masses becoming softer and cyst-like. They are lobulated owing to the fibrous bands derived from the renal capsule, and the lobules when opened may be yellowish, grayish red, or brown or blackish, and contain hæmorrhagic areas—the source of the blood which causes hæmaturia.

The larger growths are those which tend to become malignant and to produce metastases. These occur through the blood-vessels, both the arterics and veins; the bones and lungs, as previously stated, are the structures most frequently invaded, though, occasionally, extension occurs by the lymphatics, including the retroperitoneal glands.

Microscopically, they usually show a scanty stroma composed of vascularized connective tissue in columns and a parenchyma formed of endothelial polygonal or columnar, translucent nucleated cells which differ entirely from those of the renal epithelium. The cytoplasm is granular and contains, besides detritus and giant-cells, numerous fat-laden vacuoles. It is the presence of considerable fat thus disposed which first caused these tumors to be regarded as lipomata. The fat contains lecithin. Glycogen is also present; sometimes in relatively large quantities.

PROGNOSIS.—As a rule, hypernephromata grow slowly at first, months and even years elapsing before they metastasize or show other signs of malignancy. They may then progress very rapidly and, the hæmaturia becoming continuous, death occurs from exhaustion.

When the growth is thoroughly removed before this stage of malignancy is reached, it shows no tendency to recur.

TREATMENT.—An exploratory incision is warranted, as previously stated, when an abnormal growth in the abdomen or in the region of the kidney occurs coincidently with hæmorrhage, even when other symptoms of hypernephroma are not present. The majority of authorities consider this procedure advisable, even when hæmorrhage into the bladder cannot be accounted for. In some cases discomfort or tension over one kidney, and deep comparative palpation on both sides may suggest which side should be explored first, but if this unilateral examination fails to indicate the presence of a growth exploration of the other kidney is justifiable. In some instances, the organ is merely enlarged, especially toward the upper pole, or at the hilum. Removal of the growth may be performed extra-peritoneally through a lumbar incision. The fatty capsule should, according to Kuzmik, be removed along with the growth, as it may be infiltrated and thus lead to recurrence.

CANCER OF THE ADRENALS.

Primary malignant tumors of the adrenals are generally regarded as rare, but it is probable that when the symptomatology of these growths will be known by the profession at large instead of, as at present, by very few of its members many deaths now attributed to Addison's disease in adults and to asthenic disorders in children will be found to be due to this class of growths. Addison, in fact, included these neoplasms among the etiological factors of the disease which bears his name, but it is now plain that the two syndromes differ in many respects, and that the treatments indicated—medical in the one, and surgical in the other—impose the need of recognizing malignant neoplasms of the adrenals as distinct morbid entities.

VARIETIES.—Primary malignant tumors of the adrenals are of the various forms of *sarcoma* those most frequently met with

and which occur, in the majority of instances, in infancy, childhood, and adolescence; *carcinoma* which occurs, as a rule, in adults or aged subjects. Among the rarer varieties may be mentioned the *malignant hypernephroma* and a class of tumors termed by Prudden *hæmorrhagic adenoma*, i.e., the growths reviewed under the preceding heading. They appear much earlier in females than in males.

While 24 cases of malignant growths collected by Rolleston and Marks included 15 of sarcoma and 9 of carcinoma, 67 collected by Ramsay included 30 of sarcoma and 37 of carcinoma. This tends to suggest that the two forms occur about evenly.

SYMPTOMS.—As a rule, the general phenomena develop insidiously, the adrenal lesion being well advanced when they begin to appear. The strength wanes more or less rapidly; the weight gradually decreases; the pulse and cardiac action become increasingly weaker and more rapid; the temperature shows exacerbation of a couple of degrees at times, but the advanced cases are usually subnormal; the appetite decreases; digestive disturbances, such as nausea, vomiting, flatulence, and diarrhoea, are commonly observed. Anæmia is sometimes manifest, the hæmoglobin being often reduced to 50 per cent., and the red corpuscles to 3,000,000 or less. Cough, with bronchial râles, localized dullness, and hæmoptysis, are occasional complications, while dyspnoea and increase of the number of respirations are apt to occur in advanced cases. The skin may remain normal, but various degrees of pigmentation, ranging from slight icterus to actual bronzing, are observed in the majority of cases. The typical facies may alone be present in cases of primary carcinoma.

This symptomatology is based on an analysis of 60 reported cases of primary malignant tumors of the adrenals. The phenomena are clearly explained by the functions I attribute to the adrenals. Being the purveyors of the secretion which—as the albuminous constituent of hæmoglobin—sustains oxygenation and metabolism and therefore nutrition, increasing emaciation, weakness, hypothermia, the decrease of hæmoglobin, etc., are but normal results, all the other phenoma being secondary thereto. The cases in which no pigmentation of the skin occurs are usually those in which but one adrenal is involved.

All these phenomena are seldom witnessed in a single case. As a rule, after a period of progressive emaciation and adynamia, a tumor can be detected by palpation posteriorly below the costal margin, close to the vertebral column. The mass at first follows the respiratory movements and recedes under pressure, but it eventually becomes fixed and immovable. In some cases, especially in infants, the tumor cannot be detected in this manner, but the abdomen gradually enlarges with a steady increase of the line of dullness, though perhaps no other symptom be discernible. When the outline of the growth can be clearly followed with the fingers, its border is not nodular as in hepatic cancer, but smooth.

Pain is sometimes complained of; it may be located in the region of the tumor; or, radiating upward or across the back, it may extend to the shoulders. The pain has been attributed to the phrenic nerve, but a clearer explanation is the effect of the traction by the tumor, upon the sympathetic ganglia and through the greater splanchnic, upon the sympathetic chain, which is merged in with the mass of nerves, including the brachial plexus, in the tissues of the shoulders.

Pressure symptoms are apt to complicate a case of long duration. Ascites, general œdema, or œdema of the ankles or legs are commonly observed in such cases, due notably in most instances to pressure upon the inferior vena cava. Gangrene of the feet has also been observed. In carcinoma, metastasis is most common in the liver and lungs; in sarcoma it is not quite as frequent and occurs in most cases in the liver and kidney.

Death may occur suddenly, preceded by very few of the above symptoms, especially the sarcomata of infants. In the majority, however, especially in adults, the morbid symptoms gradually develop and the asthenia increases until unconsciousness, labored breathing, and coma terminate in death.

Infants may also suffer from a congenital type of adrenal tumor which simultaneously invades the liver. It is encountered as a congenital tumor, during the first weeks of life. The abdomen becomes increasingly distended; there is moderate emaciation, but no jaundice, pigmentation, ascites, or even pain, the child nursing almost up to the time of death. William Pepper²³⁰

²³⁰ Pepper: Amer. Jour. Med. Sci., Mar., 1901.

described a series of 6 cases, including a personal case, showing that congenital sarcoma of the adrenals and liver constitutes a special type of malignant disease with its own peculiar symptoms and pathological findings: Swelling of the abdomen occurred within a period ranging from birth to five weeks, thus indicating the congenital nature. The infants lived from one to sixteen weeks, thus showing great malignancy. The increase of growth could be discerned from day to day, thus illustrating rapid development. All were females. The entire normal liver structure was practically destroyed in all. The suprarenal growth exhibited the peculiarity of being very hemorrhagic. No other part of the body was involved by the new growth.

DIAGNOSIS.—The diagnosis of malignant tumor is not difficult when the tumor is sufficiently large to be discovered by palpation, especially when paræsthesia over the kidneys. This and the asthenic phenomena point clearly to the adrenals, especially if jaundice or any pigmentation of the skin be present. Unfortunately the morbid process is far advanced as a rule when these signs appear. The tumor has been mistaken for psoriasis and abscess and phrenic abscess. From hepatic cancer it differs in that the surface of the tumor is smooth instead of lobulated. Of course the possibility of metastasis in the liver, its most frequent seat, must be borne in mind. Hydatid cyst may be suggested, but the absence of the hydatid thrill and other typical symptoms will avoid error. A projecting and enlarged gall-bladder is sometimes simulated by an adrenal tumor capable of displacing the intestines anteriorly; but the latter are much less tense than such a gall-bladder. Abdominal aneurism may be suggested, but the absence of aneurismal bruit and the absence of all other signs of adrenal growth eliminate this source of error. In renal cancer or renal hypernephroma, hæmaturia and other evidences of renal disorder are usually present, while they are more likely to be absent in malignant growths of the adrenals. Pain occurs earlier than in renal tumors, while febrile disturbance is rare in the latter.

Two symptoms, according to Israel,²³¹ point to involvement of the suprarenal gland: (a) Paroxysms of pain and paræsthesias in the absence of a palpable tumor, and (b) a febrile course.

²³¹ Israel: Deut. med. Woch., No. 44, 1905.

The painful paroxysms in renal as well as suprarenal tumors are due to the extension of the neoplasm to the roots of the lumbar plexus. In suprarenal tumors this may occur quite early owing to the immediate vicinity of these structures. On the other hand, in renal tumors the invasion of the capsule usually takes place at a late period when the growth has reached so considerable a size as to become palpable. The fact that fever occurs in cases of suprarenal tumors has hitherto been unknown. Israel observed it in 57 per cent. of his cases, while in renal tumors it was present only in 1 to 2 per cent.

Another apparently characteristic fact in differentiating from renal tumor is that the adrenal growth tends to approach more nearly the median line (in the region from the seventh to the ninth costal cartilages), while the primary tumor of the kidney appears first in the region from the ninth to the eleventh. Tumor of the adrenal at the time of its presentation beneath the margin of the ribs appears broader than does that of tumor of the kidney, and the lower contour of the tumor of the adrenal is much less rounded than is that of the kidney.

The emphasis laid by Israel on the presence of fever in adrenal malignant neoplasms affords striking proof of the correctness of my contention, urged ever since 1903, that the adrenals, through the rôle of their secretion in oxidation and metabolism, were the active organs in fever—a process which pathologists have failed to explain.

Leucocythemia is sometimes simulated; but the absence of myelocytes and other characteristics soon eliminate this disease.

Ecchymosis of the orbit of unaccountable origin in infants and young children or tumor of the orbit should cause careful search for manifestations of malignant tumors of the adrenals, as previously stated.

TREATMENT.—Removal is the only resource, but as a rule the result is unsatisfactory owing to the fact that the presence of the growth is recognized only through metastasis; or when it has developed to a marked extent, and produced either through metastasis, pressure, etc., disorders in other parts of the organism which cannot be reached.

Cases in which the tumor involves one adrenal only, as suggested by the absence of symptoms of adrenal insufficiency,

marked asthenia, emaciation, hypothermia, etc., and the presence of a tumor and hyperæsthesia on one side only, offer a better chance of success, since they indicate that the other adrenal will probably be able to subserve alone the needs of the organism. The chief difficulty encountered in the course of the operation is a marked tendency to hæmorrhage owing to the friability of the morbid tissues.

CHAPTER III.

THE THYROPARATHYROID APPARATUS IN GENERAL OXIDATION AND IMMUNITY.

WE can no longer speak of the thyroid gland as a functional entity. The two external parathyroid glandules, discovered in 1880 by a Swedish physician, Sandström, and the two internal parathyroid glandules, discovered by Nicolas,¹ of Nancy, in 1893, and independently by Kohn,² of Prague, in 1895, introduced a new era in our conception of this organ. Foreign investigators, therefore, tend increasingly to adopt the term "thyroparathyroid apparatus" owing mainly to the anatomical relationship between the glandules and the thyroid vessels, with which their own circulation is directly connected. We shall see, however, that many physiological facts, the first of which were pointed out by Gley, of Paris, in 1892, and clinical observations warrant the use of this compound term.

PREVAILING VIEWS AS TO THE FUNCTIONS OF THE THYROID AND PARATHYROIDS.

In 1859, Schiff, of Geneva, found experimentally that removal of the thyroid gland in the dog caused violent nervous disorders and death. Two surgeons of the same city, the brothers J. L. and A. Reverdin, then pointed out (1882) that in certain goitrous subjects, and after the complete removal of goiter in otherwise normal subjects, there also appeared marked trophic and nervous disturbances. This was confirmed the following year by another Swiss surgeon, Kocher. The principal postoperative phenomena noted were: marked weakness and fatigue, a sensation of cold, pallor, muscular stiffness, and pains; œdematous thickening and pallor, hardness and dryness of the skin, the normal folds being more or less effaced, and loss of hair. The main nervous and mental phenomena were: tetany, sometimes attaining the violence of true tetanus and passing into

¹ Nicolas: *Bull. de la Soc. des Sci. de Nancy*, vol. v, p. 13, May 3

² Kohn: *Archiv f. mikrosk. Anat.*, Bd. xlv, S. 366, 1895.

clonic convulsions. The intelligence was also diminished, with slow intellection and enunciation as characteristic features. Paroxysms of suffocation, vertigo, syncope occurred, followed by death within a period varying from four to nine days in the vast majority of cases, the fatal ending being sometimes delayed two or three weeks beyond this period.

The brothers Reverdin termed this condition *postoperative myxædema*, while Kocher called it *cachexia strumipriva*. The term *myxædema* had already been attributed (1877) by Ord to the, now familiar, disease of which thyroid insufficiency is the predominating pathogenic factor, and which Sir William Gull had, in 1873, called "a cretinoid change."

The same phenomena were observed in the monkey by Horsley, in 1885. This observer and many others also found that the symptoms were most severe in carnivorous animals; somewhat less so in man and in the monkey; still less so in ruminants and undulates, and that they failed to occur in birds and rodents. But these experimental dissimilarities were to a great extent obliterated by the subsequent experiments of Gley, de Quervain, Hofmeister, Edmunds, and others, which showed that the variations depended mainly upon the anatomical relationship of the parathyroids and the thyroid. Thus Gley, of Paris, found, in 1892, that in the rabbit two of the four parathyroids were situated below the thyroid and were, therefore, not removed with the thyroid; while in the dog, all four parathyroids are so imbedded in the latter that it is only with great care that they can be left *in situ*.

Gley discovered another important fact: he showed that, while removal of the thyroid alone does not necessarily cause death, it was the removal of the four parathyroids which caused the nervous phenomena and the fatal ending. These observations have been sustained by many investigators, who have gradually accounted for many phenomena attributable to each organ, as will be shown in the following pages.

Removal of the thyroid only, produces morbid phenomena the severity of which depends upon the age of the animal; the younger the animal, the greater are the morbid effects witnessed, though life itself is not necessarily endangered. The animal fails to grow. The bones and epiphysial cartilages fail to

develop, the skull alone escaping; the abdomen projects and becomes larger, though relatively flabby. The testicles remain small and may fail to descend; the ovaries are also, as a rule, atrophied.

Sterility due to the non-formation of semen has been noted. Pregnant rabbits abort; hens produce very small eggs or none at all. The animal is apathetic, indifferent, dirty, awkward and apparently devoid of intelligence, and quite recalls the human cretin. The skin is rough, coarse, and squamous, being, in some, considerably creased, as in the aged, and, in others, swollen, hard, and resistant, as in myxœdema. The hair becomes coarse and shaggy, losing all luster, and tends to grow irregularly and fall. The temperature, normal at first, steadily decreases until death, the respiratory exchanges and oxidation being diminished, the nitrogen excretion likewise showing, clearly, inhibited metabolism. Anæmia, with reduction of the red corpuscles, is marked. Paralysis and convulsions may appear, but, as a rule, the animal dies cachectic after a prolonged period, the development of the trophic disorders being slow—two or three months in the most rapid cases—*i.e.*, the youngest, according to Jeandelize.

As observed by Charrin, and as will be shown later in this chapter, removal of the thyroid reduces the resistance to infections, and also, according to Lindemann, to intoxications. In man the postoperative phenomena, *i.e.*, cachexia strumipriva, rarely appears before three or four months and occasionally after a year. The same vulnerability to infections is also prominent and the sufferers are often carried away by an intercurrent infection, especially tuberculosis and pneumonia.

In full-grown subjects no marked physical changes occur, but nutrition is nevertheless impaired, emaciation, anæmia, coarseness of the skin, falling of hair, hypothermia, and other manifestations of myxœdema manifesting themselves. These phenomena are aggravated by pregnancy and lactation, repeated pregnancy and prolonged lactation having in fact been found by Morvan to favor the development of myxœdema irrespective of thyroidectomy.

On the whole, removal of the thyroid gland alone gives rise in the young: 1, to arrested growth especially marked in the

skeletal bones and sexual organs; 2, to myxœdematous thickening of the skin; and 3, to a low grade of intelligence with general apathy—as main morbid phenomena, constituting the syndromes recognized under the term cretinism; while in the full grown it causes the condition known as myxœdema.

Removal of the Parathyroids Only.—Removal of the thyroid and parathyroids causes early death, while removal of the thyroid alone, we have just seen, is followed by a prolonged postoperative life. It is to the removal of these diminutive organs, in fact, that all the nervous phenomena must be ascribed. Even when the thyroid is left *in situ*, and the four parathyroids are removed, we witness a typical syndrome: The predominant feature of the syndrome is the tendency to spasm and convulsions which may range from tetany to violent tetanic or epileptic paroxysms, with foaming at the mouth, during which the subject may die, owing to spastic immobilization of the thoracic muscles. Fibrillary tremors, tetanic and choreic movements, sufficiently violent in some cases to throw the patient to the floor are also observed. As in strychnine poisoning, the least contact evokes contractures and convulsions. Marked dyspnoea, the dominant symptom in rabbits, and paroxysms of suffocation occur both during and after the latter. The respirations are greatly accelerated, 100 to 200 times a minute in animals. Although the temperature rises during the convulsive paroxysms, it goes down considerably during the intervals, both the external and internal temperature being 4° C. or more below normal and gradually receding as death approaches. Oxygenation is deficient; the blood contains less oxygen; the red corpuscles are reduced, though the polynuclear leucocytes are increased; cyanosis is clearly shown in the rooster's comb and in the monkey. The pulse, slowed during the intervals, becomes extremely rapid and tumultuous during the convulsions. Involvement of the alimentary canal is shown by ptyalism, foetid breath, anorexia, the animal being also liable to spasm of the masseters when he attempts to take food, marked thirst, bilious and mucous vomiting, foetid diarrhoeal and bloody stools. Although the animal appears weak, somnolent, and indifferent to its surroundings, as a rule, it is sometimes terror-stricken and agitated, and seems to suffer. Pruritus is an evident

symptom. The urine is greatly reduced and abnormally toxic, especially during the convulsive and dyspnoic paroxysms; it is also markedly spasmogenic when injected into another animal. Albumin and glucose are often present; indican likewise; the chlorides and the potassium salts are present in excess; the pigments and biliary salts likewise, though their ratio tends gradually to lessen. Urea and phosphates are diminished.

These morbid effects usually begin about twenty-four hours after removal of all the parathyroids. In dogs, a single parathyroid of the four suffices in most instances to carry on their functions, but even two of them will fail to do so in some animals, removal of the other pair being followed by tetany. Death usually occurs in from three to five days after removal of all four organs; though, rarely, it does not occur until much later, forty-five days in some instances. The possibility of supplementary organs is, of course, not to be overlooked under such circumstances. As many as six parathyroids have been found at autopsies. Auerbach^{*} recently found five in an infant, but only two in 5, and but one in 8. These 13 children all showed a tendency to spasm.

Dual Function Theory.—Gley having shown the vast importance of the parathyroids, he concluded that their purpose was to supplement the function of the thyroid. The fact that the parathyroids became atrophied on removal of the latter seemed fully to sustain this view. Additional proof was seemingly afforded by the continuation of life for some time after the same procedure, the parathyroids being thus shown capable of carrying on the functions of the thyroid independently.

Contrary to this conclusion, however, was the fact, noted by Moussu and verified by Gley and also Nicolas, that the parathyroids, which became hypertrophied after removal of the thyroid, never assumed the histological structure of the latter, but retained their own. Moreover, as emphasized by Moussu, in 1893, experimental evidence pointed to the presence of two functions. This view was sustained by the discovery of two investigators, Nicolas and Kohn, working independently, of the two additional parathyroids, two only having been described by Landström, as previously stated. These two glands sufficed to

^{*} Auerbach: *Jahrbuch für Kinderheilkunde*, B. lxxxiii, Suppl., 1911.

maintain life after the thyroid and parathyroid had been removed. Vassale and Generali now obtained in the dog the complete effects of removal of the whole thyroid apparatus by extirpating only the four parathyroids, a result confirmed in the rabbit by Rouxau. Moussu then showed that extirpation of the thyroid alone was practically harmless in adult animals, but that in very young animals it was followed by experimental cretinism, while removal of the parathyroids gave rise to the nervous phenomena described in all animals, excepting, perhaps, the ox and horse.

On the whole, the prevailing view is that the parathyroids are functionally independent of the thyroid. We shall see, however, that many facts militate against this conclusion.

Effects of the Internal Secretion of the Thyroid.—Various theories as to the manner in which the thyroid carries on its functions have been vouchsafed, but all have succumbed to the view that the organ secretes some substance which finds its way into the blood, *i.e.*, that it produces an internal secretion. This was suggested a century ago by the experimental work of King, of London, who found that the colloid substance of the gland passed into the lymphatics, an observation confirmed by Hurthle, Baber, Sir Victor Horsley, and others.

That the organ is a secreting one is shown by the fact that it can be transplanted or grafted from its normal site to other parts of the body. Grafting was first successfully performed by Schiff, and repeated by many other investigators, including von Eiselberg, but notably by Christiani, of Geneva. Very uncertain at first, the method was, however, so perfected by the latter experiments that success now attends every operation. It consists in inserting not a whole lobe, as had been previously practised, but small fragments. After a time there is produced *in situ* a nest, as it were, of typical thyroid tissue capable of carrying on the functions of the original gland. Moreover, this tissue seems capable of doing by means of its secretion what the thyroid tissue proper cannot do, *viz.*, to protect the animal against tetany. Louis Morel^{2a} recommends intraperitoneal, intrasplenic and intraosseous grafts as the most satisfactory.

Again, extracts of the gland, the gland itself, in its raw

^{2a} Louis Morel: *Archives génér. de chirurgie*, May, 1912.

state or desiccated, antagonize the morbid effects of thyroideectomy. This was first shown by Vassale, who found that the intravenous injection of aqueous extract of thyroid controlled temporarily these phenomena. This experiment was the starting point of Murray's memorable introduction of the use of thyroid preparations in myxedema in all its forms. In toxic doses, thyroid extract was found by Ewald, Fenwick, Haskovec, and many others to cause: rapid emaciation, marked vasodilation, a rapid pulse, diuresis, acceleration of the lymphatic circulation, hypothermia, polypnea, polyphagia, polydipsia, glycosuria, excessive excretion of nitrogenous wastes, soon followed by extreme depression, anorexia, vomiting, loss of reflexes, paralyses, convulsions, and death—all phenomena which may be evoked in man by injudicious thyroid medication.

A feature worth retaining, in view of conclusions to be submitted later, is that many observers, including Treupel, Ord, and Ver Eeke, have laid stress upon the correlation of the thyroid functions with general nutrition. Not only is there increased elimination of nitrogenous and other tissue wastes, but, as emphasized by Magnus-Lévy, the respiratory exchanges, including, of course, the intake of oxygen, are greatly increased. Moreover, Vassale and Generali⁴ advanced the view, quite compatible with all these biochemical observations and with the known effects of the thyroid extracts in cretinism and myxedema, that the thyroid secretion served to activate metabolic processes, both in the cutaneous tissues and in the organism at large.

Effects of the Internal Secretion of the Parathyroids.—Removal of these organs being followed by spasm and convulsions, the normal conclusion at once suggested itself that their purpose was to destroy spasmogenic poisons produced within the body. Indeed, the blood of dogs subjected to parathyroidectomy was found by Rogowitsch and others to be toxic and to cause convulsions in normal animals, while Laulanié and others found the urine also toxic. The liver, according to Morel and Rathery,⁵ shows acidosis degeneration, while Morel^{5a} and Werelius^{5b} found

⁴ Vassale and Generali: Arch. ital. de biol., vol. xxxii, p. 154, 1900.

⁵ Morel and Rathery: Jour. de physiol. et de path. gén., Sept., 1912.

^{5a} Morel: La gynécologie, April, 1912.

^{5b} Werelius: Surgery, Gynecol. and Obst., Feb., 1913.

that parathyroidectomy enhances the liability of pregnant animals to autotoxic convulsions.

The injection of parathyroid extract was found to antagonize the convulsive disorders caused by the extirpation of all parathyroids by Moussu and other observers, but the beneficial effects lasted a short time only, the animals dying nevertheless. As shown by Vassale, the same beneficial effects are obtained by the injection of thyroid extract. Transfusion of a normal dog's blood to that of one deprived of its thyroid and parathyroids was also shown by Fano and Zanda to palliate considerably the convulsive phenomena. Still, the fact that parathyroid extract arrests the latter temporarily has generally been accepted as proof that the parathyroids contribute independently of the thyroid some anti-toxic substance to the blood.

Of experimental and clinical interest in this connection, however, are the observations of Macallum and Voegtlin,^{5c} and Macallum,^{5d} that calcium salts given by the mouth or hypodermically inhibit the tetany due to removal of the parathyroids, both in man and in lower animals, apparently restoring them completely. This suggests that it is by influencing in some way calcium metabolism that the parathyroid secretion produces its antitoxic effects.

OBSCURE FEATURES OF THE THYROPARATHYROID PROBLEM.

As the foregoing review of the status of the question indicates, much valuable work has been contributed toward its elucidation. Yet if we ask what the functions of the thyroid and parathyroids are in the economy, it must be admitted that none of the data or conclusions available answer the question. Growth and mental development are prevented by arrest, either through organic inhibition of the functions of the thyroid or through removal of this organ. What function does it carry on that enables it to influence so fundamentally the welfare of the entire organism? Vassale's view that the thyroid secretion serves to hasten tissue metabolism is a self-evident conclusion sustained by the symptomatology of and the use of thyroid preparations in myxedema and cretinism, but it does not tell

^{5c} Macallum and Voegtlin: Johns Hopkins Hosp. Bull., Mar., 1908.

^{5d} Macallum: Jour. of the Am. Med. Association, Aug. 3, 1912.

us *how* it fulfills this function, *i.e.*, what its secretion does to incite and sustain it.

In the preceding chapter, I filled the corresponding gap in respect to the adrenals by tracing the adrenal secretion to the pulmonary alveoli, and showed that it was converted into adrenoxidase in this location, and that it served, through the intermediary of the red corpuseles, to sustain oxidation, metabolism, and nutrition. What is the corresponding itinerary of the thyroid secretion? Accepting the prevailing and irrefutable view that the latter does sustain metabolism, what is the functional relationship between the thyroid and the adrenals? Again, we find that removal of the thyroid, as does that of the adrenals, predisposes greatly to infection. In virtue of what property does the thyroid secretion contribute to the protection of the body against infectious diseases? These and many other questions have not as yet been answered.

The field of the parathyroids is at least as replete with obscure factors. The same lack of knowledge concerning the itinerary of their secretion, its relationship with the blood, and the actual rôle it fulfills prevails. The salient postoperative effects being convulsive disorders of various types, we are again brought to the necessity of attributing to these organs a very active participation in the autoprotective resources of the body, the poisons antagonized being no longer toxins, but, apparently at least, toxic products of metabolism, *i.e.*, spasmogenic intermediate wastes. Here, again, we find ourselves confronted with an active sway over metabolism or, better perhaps, catabolism. Indeed, the importance of this attribute is of major importance in the practical field. As Parhon and Golstein^a write: "Certain pathological states, such as pregnancy, parturition, lactation, certain disorders of the female genital apparatus, certain diseases of the thyroid, can facilitate the appearance of tetany, which under these conditions is probably of parathyroid origin." As to the present status of the question, the same authors conclude (1909) "that the intimate mechanism of the production of parathyroid tetany—as well as other forms of tetany—has not as yet been elucidated. The data we possess for the time being

^a Parhon and Golstein: "*Les Sécrétions Internes*," p. 209, Paris, 1909.

cannot but indicate the path that researches still necessary should follow to solve the question."

THE THYROPARATHYROID SECRETION AS AN OXIDATION ACTIVATOR THROUGH ITS ACTION ON CELLULAR PHOSPHORUS.

Verworn,⁷ referring to Max Schultze's observation that the phosphogenic cells of lightning bugs absorb oxygen actively, quotes approvingly Pflüger's statement concerning this process: "Here, in the wonderful spectacle of animal phosphorescence, nature has given us an example that shows where the taper burns that we call life." If, on the other hand, we recall Hutchison's⁸ remark: "Briefly then, it may be said that the effect of the administration of the thyroid is to increase oxidation in the body; it makes tissues, as it were, more inflammable, so that they burn away more rapidly" and also the fact that iodine when brought into contact with phosphorus causes ignition of the latter, the meaning of the above heading will be apprehended. Briefly, from my viewpoint, *the iodine in organic combination which the thyroparathyroid secretion contains renders the phosphorus of all tissue cells, and particularly their nuclei, more prone to undergo oxidation by the adrenoxidase of the blood.* Hence the great influence of the thyroid gland on oxidation, on the vital process itself, on development, physical and mental, as is well shown by the results of thyroid preparations in cretinism and other kindred disorders.

In the earlier editions of the present work, I advanced the view that it was in part through the adrenals that the thyroid secretion produced its effects, and that, conversely, "cachexia strumipriva," i.e., the myxœdema which follows removal of the thyroid, was "partly a consequence of adrenal insufficiency." This view, which makes oxidation the common aim of two sets of organs, suggests itself when the effects of extirpation of the thyroid are compared with those following removal of the adrenals. Both postoperative syndromes include central and peripheral hypothermia, lowering of the blood-pressure, dyspnoea, cyanosis, accelerated respiration, weakness and increased rapidity

⁷ Verworn: "General Physiology," Amer. ed., p. 255, 1899.

⁸ Hutchison: Brit. Med. Jour., July 16, 1898.

of the heartbeat and pulse, muscular weakness, mental torpor, melancholia, muscular rigidity, convulsions, coma, and death; even bronzing is sometimes witnessed in the advanced stages of myxœdema. Conversely, the effects of thyroid preparations strikingly recall those awakened by the adrenal secretion. Beebe,⁹ for example, while acknowledging that it is not known "on what tissue or set of tissues the thyroid secretion acts," states: "We know that it is connected in some way with the function of oxidation in the body. By the administration of thyroid to a cretin or a patient with myxœdema, it is possible to increase the absorption of oxygen from 20 to 75 per cent. There is a corresponding increase in the amount of heat given off from the body. The removal of the thyroid in an animal will cause diminution in the absorption of oxygen, which may be again increased by thyroid feeding. Administration of thyroid to a normal animal will cause an increase of from 10 to 40 per cent. in the oxygen demand."

All this naturally suggests a mutual stimulation between the thyroparathyroid apparatus and the adrenals. In 1903, I advanced the view that the thyroid secretion directly or indirectly increased the adrenal secretory functions.

Experimenters who have taken up the question have also been led independently to the conclusions I had previously reached.¹⁰ That experimental thyroidectomy should produce no histological changes in the adrenals, as was observed by Hofmeister,¹¹ Bensen,¹² Bruckner,¹³ and others, is self-evident, unless the adrenals be endowed with compensative functions, which has never been demonstrated. But it is when hyperactivity of the thyroid is used as the basis of the inquiry that such a functional relationship between the two sets of organs shows itself. While, for example, normal blood has no mydriatic power, injections of thyroid extract confer this property of the adrenal secretion upon it, owing, according to Kraus and Friedenthal¹⁴ and Caro,¹⁵ to stimulation of the adrenals. Kostlivy¹⁶ also

⁹ Beebe: *Jour. of the Amer. Med. Assoc.*, Mar. 4, 1911.

¹⁰ Sajous: "Internal Secretions and the Principles of Medicine," vol. 1, 1st ed., p. 152, 1903.

¹¹ Hofmeister: *Beiträge z. klin. Chir.*, Bd. xi, S. 463, 1894.

¹² Bensen: *Virchow's Archiv*, Bd. clxx, S. 229, 1902.

¹³ Bruckner: *Comptes-rendus de la Soc. de biol.*, vol. lxxiv, p. 1123, 1908.

¹⁴ Kraus and Friedenthal: *Berlin klin. Woch.*, Bd. xiv, S. 1710, 1908.

¹⁵ Caro: *Med. Klinik*, Berlin, Bd. vi, S. 136, 1900.

¹⁶ Kostlivy: *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, Bd. xxi, Nu. 4, 1910.

observed in a large number of cases of thyroid intoxication that the blood-serum produced dilatation of the pupil, while thyroidectomy caused this power markedly to decline. The same mydriatic activity was conferred on the serum of animals by giving thyroid extract by the mouth, the mydriatic power corresponding with the dose administered. Hoskins,¹⁷ who refers to the above observations, obtained similar results in guinea-pigs. In both exophthalmic goiter and myxœdema, as we shall see, the participation of the adrenals in the processes shows itself in various ways. Physiology and clinical medicine thus unite in showing that the secretion of the thyroid apparatus enhances the functions of the adrenals. I might, however, express this in a different term. Starling¹⁸ has named "hormone" (from ὁρμαω, arouse or excite) a substance which, originating in one organ, is capable of stimulating another. Internal secretions being included among the hormones, we can state that the hormones produced by the parathyroid apparatus are capable of stimulating the adrenals. That the thyroid secretion does not serve only for this purpose, however, is suggested by the fact that it is component of the blood at large. We can only, therefore, look upon its exciting effect upon the adrenals as an incidental feature of a general function.

What is the nature of this function? We have seen that the prevailing views afford no answer to this question. We are, therefore, brought back to the answer I submitted at the beginning of this section, viz., that "iodine in organic combination which the thyroparathyroid secretions contain renders the phosphorus that all tissue-cells and particularly their nuclei contain more prone to undergo chemical change, i.e., oxidation in this connection, with the adrenal product adrenoxidase as its source of oxygen," and to analyze the evidence which led me to it. The plan adopted for the same purpose in the case of the adrenals will be carried out, viz., to submit the main evidence in detail, though in as terse a form as possible. Starting with the nature of the thyroparathyroid secretions, I shall then trace their itineraries throughout the organism as an organic compound, and finally its function.

¹⁷ Hoskins: Amer. Jour. of Physiol., vol. xxvi, p. 426, 1910.

¹⁸ Starling: "Recent Advances in the Physiology of Digestion," 1906.

The thyroid product is an "iodized globulin" (as Oswald maintains), the globulin being the albuminous constituent of hæmoglobin, i.e., adrenoxidase.

As Notkin¹⁹ and also White and Davies²⁰ hold, the action of the thyroid secretion resembles that of an organized ferment. The identity of this ferment suggests itself, i.e., the adrenal active principle, when we consider Baumann's analyses of his thyroidin. Among other tests, for example, he found that it was practically insoluble in ether and chloroform; that it was not destroyed by digestive ferments, and that it stood a temperature of 100° C.²¹ These are the specific tests of adrenalin. That this active principle, in turn, occurs as a constituent of what I have termed "adrenoxidase," is shown by the fact that it also gives the tests of the plasmatic oxidase; Lépine, for example, found that the thyroid secretion contained an oxidase which gave the blue reaction with tincture of guaiac. Again, we have seen that adrenoxidase is a globulin: Oswald termed his product "thyroglobulin" and described it as an "iodized globulin." Again, adrenoxidase being the oxidizing constituent of the blood, and circulating as it does in all tissues and organs, as the albuminous portion of the hæmoglobin, it must necessarily circulate also in the thyroid and parathyroids as a blood constituent, and out of which the secretions of these organs obtain it.

The actual presence of an oxidizing ferment was further confirmed recently by Youchtchenko.²² Under the heading of "oxidizing ferments" of the thyroid gland, he states that this organ is "rich in catalases." As I have shown in the preceding chapter, catalysis is a property of the adrenal active principle. He found, moreover, that "the catalase, as well as the oxidizing ferment, is contained in the red blood-corpuscles." This corresponds precisely with the fact I pointed out several years ago in the first edition of the present work. In keeping also with what I had held concerning the influence of the thyroid on oxidation (partly through its influence over the adrenals), Youchtchenko found that in dogs "thyroidectomy was invariably followed by a manifest, at times considerable, lowering of the

¹⁹ Notkin: Wiener med. Woch., Bd. xlv. S. 824 u. 872, 1895.

²⁰ White and Davies: Cited by Halliburton: Practitioner, Jan., 1897.

²¹ Cited by Morat and Doyon: Traité de physiologie, vol. i. p. 467, 1904.

²² Youchtchenko: Archives des Sciences Biologiques de l'Institut Impérial de Médecine Expérimentale à St. Petersburg, Tome xv, Nos. 3 and 4, p. 173, 1910.

temperature"; "in two dogs," he adds, "this oxidizing power fell almost to one-half of the normal."

Yet in the light of the functions I have ascribed to the adrenals, and the functional stimulation these organs receive from the thyroid product, these effects upon the temperature should correspond with a reduction of the oxyhæmoglobin, the active agent of which is adrenoxidase. That such is the case is shown by the experiments of Albertoni and Tizzoni,²³ who found that removal of the thyroid caused the blood to show *decreased power to fix oxygen*; while Masoin²⁴ found that the relative quantity of *oxyhæmoglobin* in the blood was diminished gradually as the postoperative phenomena of thyroidectomy progressed.

Another constituent of thyroiodin may be regarded much in the same light, viz., nucleoproteid. Sherrington, Milroy and Malcolm,²⁵ and others have found that the granulations of the most numerous leucocytes in the blood, the neutrophiles, are composed of nucleoproteid, while the observations of Bail, Stokes, and Wegefarth,²⁶ Sangr  e,²⁷ and others have as clearly shown that these granulations leave the periphery of the cell. We shall see in the next volume that it is through these cells that nucleoproteid reaches the thyroid apparatus. As stated by Beebe,²⁸ "chemical studies of the gland have demonstrated the presence of three forms of proteid: nucleoproteid, globulin, and albumin, in addition to a number of simpler cleavage products of proteid, the latter being bodies of no especial significance. The normal thyroid contains relatively little of the nucleoproteid, much globulin, and a smaller amount of albumin; the parathyroid, on the other hand, contains a large amount of nucleoproteid, a very small proportion of globulin, and still smaller amounts of albumin." Here, again, we find in the secretion a supposed intrinsic component, nucleoproteid, which, in reality, is but a commonplace, though important, constituent of the blood.

That iodine is the active agent of the thyroparathyroid secretions is now absolutely established. Some observers have

²³ Albertoni and Tizzoni: Cited by Maragliano: *Gaz. degli Ospedali*, Oct. 20, 1894.

²⁴ Masoin: *Bulletin de l'Acad  mie de M  decine de Belgique*, No. 1, p. 88, 1895.

²⁵ Milroy and Malcolm: *Jour. of Phys.*, vol. xxv, p. 106, 1899.

²⁶ Bail, Stokes, and Wegefarth: *Bull. Johns Hopkins Hosp.*, Dec., 1897.

²⁷ Sangr  e: *Phila. Med. Jour.*, Mar. 12, 1898.

²⁸ Beebe: *Jour. Amer. Med. Assoc.*, Mar. 4, 1911.

held that the thyroid and parathyroids contain no iodine, in opposition to the findings of many authorities, but this must be ascribed to defective analytic work. Beebe, while stating that "the physiologically active portion of the gland secretion is a protein substance containing iodine in a specific organic combination," also remarks: "I have never been able to obtain a definite protein or proteose from the thyroid absolutely free of iodine." Quantities of iodine varying from 2.05 to 13.04 mg. per gland have been found by Baumann, Weis, Oswald, Rosetzki, Iolen, Gley, and others, in Europe, and Wells (10.79 mg.), in this country. Moreover, "if potassium iodide be given to an animal, there is an increase in the content of the physiologically combined iodine in the gland." As Oswald holds, therefore, the thyroid product is an "iodized globulin."

Again, as stated by Parhon and Golstein²⁹ in their recent work (1909) referring to the identity of the thyroid product, "Fortunately we are today better informed concerning the functions of the thyroid body, and if we cannot exclude the production of certain enzymes by the thyroid cells we can, on the other hand, affirm that their principal action is due to a more clearly defined substance, which is an iodized globulin."

The foregoing analysis has shown that in keeping with the prevailing view the active principle of the thyroparathyroid secretions is iodine; but inasmuch as its activity in this organic combination exceeds greatly that of iodine or its salts, a property which its combination with a ferment (adrenoxidase) explains, its true identity is more accurately expressed by the term "*thyroidase*," which I suggested some years ago.

Why should this combination occur? We will see presently that its purpose is primarily to insure the absorption of the iodine by the red corpuscles, hæmoglobin being the normal host of these cells. Analysis of this question showed that

The thyroid and parathyroid secretions ultimately reach the superior vena cava and are carried to the pulmonary alveoli, where they combine and are taken up by the red corpuscles, along with the adrenal secretion.

Kjng, over a century ago, traced the thyroid secretion to the lymphatics, and Hürthle showed that fluids as well as their

²⁹ Parhon and Golstein: "Sécrétions Internes," p. 16, Paris, 1909.

colloid passed from the thyroid vesicles to these vessels, a fact confirmed by Horsley and others. Baber found colloid similar to that in the thyroid within the lymphatic vessels. The more recent investigations of Biondi,³⁰ Zielinska,³¹ Vassale and de Brazza³² on the thyroid, and those of Welsh,³³ and Capobianco and Mazziato,³⁴ and others on the parathyroids, have shown that the product of these organs passes into the perivascular lymph-spaces. Being then transferred to the larger cervical lymphatics, they are discharged by the right and left lymphatic ducts—the thoracic duct, according to Pembrey³⁵—into the subclavian veins, and by way of the superior vena cava to the heart. Here they become merged with the venous blood of the entire organism, *forming a single secretion*, which is then inevitably carried to the heart, and thence to the lungs. As the venous blood carrying the adrenal secretion passes from below to these organs to be oxygenized, so is the thyroparathyroid secretion carried from above to the air-cells.

All these facts tend to controvert the current view that the thyroid and parathyroids are not functionally related. The fact is that the prevailing opinion, referred to on p. 147, is not based on a broad view of the evidence in the case. My own conception sustains and completes that of Gley, which admits a functional association in the sense that one set of organs serves to complete the work of the other. This intimate connection is shown by the observation of Edmunds that, while extirpation of the parathyroids causes histological changes in the thyroid, removal of the latter also causes degeneration of the parathyroids. Moreover, Vassale and Generali³⁶ found that after death from removal of the latter the thyroid contained no colloid. Lusena³⁷ noted the same fact, thus showing that the formation of the thyroid secretion depends in some way upon the functions of the parathyroids. Edmunds emphasized this fact by showing that hypertrophy of the thyroid followed parathyroidectomy, both embryonic tissue and vessels showing development. This survival

³⁰ Biondi: Berl. klin. Woch., Bd. xxv, S. 954, 1888.

³¹ Zielinska: Virchow's Archiv, Bd. cxxxvi, S. 170, 1894.

³² Vassale and de Brazza: Arch. ital. di biol., vol. xxiii, p. 292, 1895.

³³ Welsh: Jour. of Anat. and Physiol., Apr., 1898.

³⁴ Capobianco and Mazziato: Giorn. Int. de Sci., Nos. 8, 9, and 10, 1899.

³⁵ Pembrey: Hill's "Recent Advances in Physiology," p. 579.

³⁶ Vassale and Generali: Riv. di Patol. Nerv. et Ment., vol. i, pp. 95 and 249, 1896.

³⁷ Lusena: Fisiopatologia dell'Appar. Tiro-parat., Florence, 1899.

suggests that removal of the parathyroids is not as fatal as generally believed. Indeed, Gley³⁸ had two dogs survive removal of all the parathyroids leaving only one lobe of the thyroid; the same operation in two other dogs and in a cat was followed by disturbances which became fatal on removing the remaining thyroid lobe. In another dog parathyroidectomy caused only trophic disturbances and death in one month. The same thing was observed in rabbits when two parathyroids only were left. Edmunds³⁹ also had two survivals in dogs after parathyroidectomy and deems this operation less grave than thyroidectomy, an opinion which is also Gley's.

Again, Halpenny,⁴⁰ after a comprehensive series of experiments in the same direction, writes: "I have been unable to confirm the statement that complete parathyroidectomy invariably proves fatal, and that in a short time. In dogs 3 and 7, where serial sections of the thyroid removed post-mortem showed no parathyroid, the animals lived 30 and 27 days, respectively, without symptoms and were killed. In dog 1, symptoms did not occur, and at the post-mortem no parathyroids were found, although serial sections were not cut. In cats 1, 6, and 8, in which at the operation the thyroid lobe with the parathyroids on one side, and the parathyroids alone on the other side, were removed, the animals lived, without symptoms, 23 days, 25 days, and 30 days, respectively, and were then killed. In all three cases a careful post-mortem search was made, and the remaining lobe of the thyroid was cut in serial sections, and no traces of parathyroid was found. There is a tendency to disregard these exceptions—MacCallum and Davidson,⁴¹ Berkeley and Beebe⁴²—and explain them by supposing that parathyroids have remained behind unobserved." This explanation is hardly tenable in view of the numerous examples presented. As to accessory glands, as Vincent⁴³ states, "If accessory glands be so usually present, the question as to the importance to life of these glands ceases to have the value hitherto attached to it." Although I believe Halpenny killed his animals too soon after the operation, Parhon

³⁸ Gley: *Brit. Med. Jour.*, Sept. 21, 1901.

³⁹ Edmunds: *Jour. of Pathol. and Bacteriol.*, Jan., 1896.

⁴⁰ Halpenny: *Surgery, Gynecology, and Obstetrics*, May, 1910.

⁴¹ MacCallum and Davidson: *Medical News*, Apr. 8, 1905.

⁴² Berkeley and Beebe: *Journal of Medical Research*, Feb., 1909.

⁴³ Vincent: *London Lancet*, Aug. 11 and 18, 1906.

and Golstein⁴⁴ having observed postoperative death (though without tetanic phenomena) as much as 30 and 66 days after thyroparathyroidectomy in the cat, the fact remains that added to the data recorded by Gley his evidence tends to weaken the view that the parathyroids are endowed with independent functions. Swale Vincent, in his recent book (1913), adduces convincing data indicating "an intimate relationship between the two structures," anatomical, physiological, and pathological.

Finally, and pointedly suggesting a combined function, we have seen that a transplanted or grafted piece of thyroid tissue, free of all parathyroid tissue, assumes the functions of both sets of organs, arrests the convulsive disorders due to extirpation of the parathyroids alone, and prevents death.

All this clearly points to a functional connection (probably a nervous one to co-ordinate the relative proportions of their secretions) between these two sets of organs, and thus insures the ultimate formation in the lungs of a perfect, *i.e.*, physiological, thyroparathyroidal product.

The purpose of this itinerary suggests itself when we recall that, as stated by Nothnagel and Rossbach,⁴⁵ hæmoglobin can fix large quantities of iodine. It accounts also for the fact that Gley⁴⁶ and Bourcet found iodine in the red corpuscles. Being a component of the albuminous hæmoglobin of these cells with adrenoxidase, however, iodine should be found in all tissues. While Bourcet⁴⁷ ascertained that such was the case, Justus⁴⁸ found it in all cellular nuclei, so rich as is well known in phosphorus. This simultaneous presence of iodine and phosphorus in the nuclei, and also of iodine in the red corpuscles, suggests the nature of process carried on in the cells: *viz.*,

The thyroparathyroid constituent of the hæmoglobin enhances oxidation by increasing, as a ferment, the vulnerability of the phosphorus, which all cells, particularly their nuclei, contain, to oxidation by the adrenoxidase in the blood.

This action is strikingly shown by the fact that iodine, the active constituent of the thyroid secretion, and its salts, as shown by Henrijean and Corin,⁴⁹ Handfield Jones,⁵⁰ and others, cause

⁴⁴ Parhon and Golstein: "Sécrétions Internes," pp. 607 and 609, Paris, 1899.

⁴⁵ Nothnagel and Rossbach: "Thérapeutique," p. 261, 1889.

⁴⁶ Gley: La Semaine médicale, May 25, 1898.

⁴⁷ Bourcet: Cited by Morat and Doyon: Traité de physiologie, i, p. 470, 1904.

⁴⁸ Justus: Virchow's Archiv, Bd. cxxxvi, S. 1, 1904.

⁴⁹ Henrijean and Corin: Arch. de pharmacodyn., ii, 1896.

⁵⁰ Handfield Jones: Cited by Wood: "Therapeutics," 13th ed., p. 499, 1906.

excessive elimination of phosphates and phosphoric acid, and that thyroid preparations, according to Roos, Scholtz,⁵¹ Pouchet,⁵² and others, act in the same way. "Emphasis must be laid," writes Chittenden,⁵³ "upon the apparent connection between the thyroid gland and phosphoric acid metabolism," giving as example "the increased excretion of P_2O_5 after feeding thyroids to normal animals, and the great decrease in the case of animals with the thyroids removed."

The untoward effects of large doses of thyroid preparations on the nervous system, owing to its wealth in phosphorus and fats, as manifested by tremor, tachycardia, optic neuritis (Coppez⁵⁴), etc., also bespeak a marked influence on this element: Cyon,⁵⁵ in fact, found that injections of iodothyrim excited the depressor nerve directly to such a degree that the vascular pressure often declined to two-thirds of the normal.

A familiar action of the thyroid preparations is a rapid reduction of fat in obese subjects when full doses are administered. The presence in the fat-cell of a nucleus rich in phosphorus whose purpose is promptly to promote oxidation of the fat when the organism requires additional carbohydrates explains this action. Schöndorff⁵⁶ found that the reserve fats could be exhausted before the nitrogenous tissues were affected.

The mode of action of the thyroid active principle, iodine, is suggested by the presence of this halogen in all nuclei, as shown by Justus⁵⁷ and others. This means that iodine is found wherever phosphorus is present, while, as shown above, it is most active where phosphorus is known to be most plentiful. Now, chemistry furnishes, as previously stated, a clue to the manner in which the phenomena I have enumerated occur: "If a fragment of phosphorus lying on a plate is sprinkled with iodine," writes Wilson,⁵⁸ "the substances unite, and heat enough is produced to kindle the phosphorus." Nitrogen, hydrogen, and chlorine are ubiquitous constituents of our tissues, and the vigorous explosives they form with phosphorus and the intense

⁵¹ Scholtz: *Centralbl. f. inn. Med.*, Bd. xvi, S. 1041, 1069; 1895.

⁵² Pouchet: *Bull. gén. de thérap.*, Sept. 15, 1905.

⁵³ Chittenden: *Trans. Cong. Amer. Phys. and Surgs.*, iv, p. 93, 1897.

⁵⁴ Coppez: *Arch. d'Ophthal.*, Dec., 1900.

⁵⁵ Cyon: *Arch. de physiol.*, x, p. 618, 1898.

⁵⁶ Schöndorff: *Arch. f. d. ges. Physiol.*, lxxiii, S. 423, 1896; lxxii, p. 395, 1897.

⁵⁷ Justus: *Loc. cit.*

⁵⁸ Wilson: *Inorganic Chemistry*, p. 234, 1897.

liberation of heat the reactions entail are familiar features of the laboratory. Roos⁵⁹ found that in a dog in nitrogenous equilibrium iodothylin "caused at once a marked increase in the output of sodium, sodium chloride, and phosphoric oxide."⁶⁰

Finally, as stated in the italicized postulate, "the thyro-parathyroid constituent of the hæmoglobin enhances oxidation by increasing, as a ferment, the vulnerability of all cells" to the action of adrenoxidase. That is shown by many facts.

Chantemesse and Marie, Ballet and Enriquez,⁶¹ Bourneville,⁶² Shattuck,⁶³ Lorand,⁶⁴ and many other clinicians, including myself, have noted that thyroid preparations caused a rise of temperature of several degrees. These observations are controlled by those of Stüve and Thiele and Nehring,⁶⁵ that thyroid extract increases over 20 per cent. the oxygen intake and to nearly as great a degree the carbonic acid output. This is evidently produced by the active agent of the thyroid secretion, iodine, for this halogen itself increases oxidation as well. Thus, Rabuteau, Milanese, and Bouchard,⁶⁶ Henrijean and Corin⁶⁷ have all noted an increase of nitrogen excretion. Wood⁶⁸ and Cushny⁶⁹ state, in fact, that iodine can produce fever. Heinrich Stern^{69a} noted a rise of temperature at times of 3° F. in cases of hyperthyroidia.

Removal of the thyroid, on the other hand, lowers oxidation. Albertoni and Tizzoni, and Magnus-Levy⁷⁰ found, for example, that this procedure decreased markedly the output of carbon dioxide, and that it caused hypothermia. The fall of temperature is gradual, according to Lorrain-Smith,⁷¹ and most marked, according to Rouxeau,⁷² at the end of the operation. The proportion of red corpuscles is reduced, according to Moussu.⁷³ Reverdin observed in man that the hæmoglobin was also diminished, while Horsley noted increased sensitiveness to cold.

⁵⁹ Roos: *Münch. med. Woch.*, No. 47, S. 1157, 1896.

⁶⁰ Cited by Chittenden: *Loc. cit.*, p. 98.

⁶¹ Ballet and Enriquez: Cited by Popoff: *Arch. gén. de méd.*, Oct., 1899.

⁶² Bourneville: *Arch. de neurol.*, Sept., 1896.

⁶³ Shattuck: *Boston Med. and Surg. Jour.*, June 30, 1904.

⁶⁴ Lorand: *Lancet*, Nov. 9, 1907.

⁶⁵ Thiele and Nehring: *Zeit. f. klin. Med.*, xxx, S. 41, 1896.

⁶⁶ Bouchard: *C.-r. de la Soc. de Biol.*, pp. 227, 237, 1873.

⁶⁷ Henrijean and Corin: *Arch. de pharmacodyn.*, II, 1896.

⁶⁸ Wood: "Therapeutics," 13th ed., p. 499, 1906.

⁶⁹ Cushny: "Pharmacology and Therapeutics," 4th ed., p. 514, 1906.

^{69a} Stern: *Archives of Diagnosis*, July, 1911.

⁷⁰ Magnus-Levy: *Zeit. f. klin. Med.*, Bd. xxxiii, S. 269, 1897.

⁷¹ Lorrain-Smith: *Jour. of Physiol.*, vol. xvi, p. 378, 1894.

⁷² Rouxeau: *Arch. de physiol.*, vol. xxix, p. 136, 1897.

⁷³ Moussu: *C.-r. de la Soc. de Biol.*, p. 772, 1903.

Albertoni and Tizzoni and Masoin found that the blood contained less oxygen than normally.

This applies as well to removal of the parathyroids, which was found by Jeandelize⁷⁴ also to lower the temperature. That the thyroid apparatus can itself raise the temperature, is shown by the febrile process and sense of heat with flushing observed in the sthenic stage of exophthalmic goiter, *i.e.*, when the thyroid apparatus is still overactive. When thyroid extract is given to such cases, the exchanges may be increased to a surprising degree—77 per cent. in a case observed by Hirschlaß.⁷⁵ The disease may in fact be brought on by thyroid preparations, as noted by Notthaft⁷⁶ and other clinicians.

Still, as Chittenden states,⁷⁷ "according to Baumann, doses of 1 milligramme of iodothylin, which contain only 0.1 milligramme of iodine, will produce a decided effect upon a goiter after three or four applications, thus clearly indicating that it is not the iodine *per se* that is effective, but rather the iodine compound." This will recall the observations of Notkin and White and Davies that the action of the adrenal secretion resembles that of an organized ferment, and my own that the adrenal principle with which the iodine is combined endows it with the properties of a ferment, the purpose being probably to increase the activity of the iodine on the cellular phosphorus.

THE THYROPARATHYROID SECRETION AS WRIGHT'S OPSONIN.

Fraenkel isolated from the thyroid what he termed a "thyroantitoxin," which he thought served to neutralize in the gland itself toxic substances brought to it by the blood. Notkin also separated a substance he called "thyroproteid," a product of tissue exchanges which he believed reached the organ, to be destroyed therein by a ferment, thyroidin, formed locally. These and all other theories, including Blum's, which restrict the antitoxic process to the gland itself have not stood the test of time. These conceptions are now only of historical interest, many investigators having shown that whatever function the thyroparathyroid apparatus may carry on should be attributed

⁷⁴ Jeandelize: "Insuffisance thyroïdienne et parathyroïdienne," p. 45, 1903.

⁷⁵ Hirschlaß: *Zeit. f. klin. Med.*, Bd. xxxvi, Nu. 3-4, S. 200, 1898-99.

⁷⁶ Notthaft: *Centralbl. f. inn. Med.*, Apr. 9, 1898.

⁷⁷ Chittenden: *Loc. cit.*, p. 99.

to the passage of its secretion into the blood, in which its active principle, in organic combination, has been found by Gley, Bourget, and others, both in man and the lower animals. The evidence submitted in the foregoing pages fully sustains this position.

What the prevailing views are concerning the rôle of the thyroid secretion, and what my own researches represent in respect to them, may be graphically illustrated by quoting the recently published words of Youchetchenko, of the Institute of Experimental Medicine of St. Petersburg.⁷⁸ "Some suppose that it [the secretion of the thyroid] is necessary for the development of the bones, the digestion, the nervous system, etc.; others express the opinion that it fills the rôle of antitoxin, which renders non-toxic the toxic products of nutritional exchanges; others, finally, affirm that the toxic substances elaborated in the economy are transformed, under the influence of the ferment in the thyroid, into substances necessary and even indispensable to the life of the organism."

If the function I ascribe to the thyroid apparatus was clearly defined in the foregoing pages, it will be seen that they harmonize all those outlined by Youchetchenko. The labilizing or sensitizing action I attribute to the iodine (in organic combination) on tissue phosphorus explains the action of the thyroid product upon "the development of bones, the digestion, the nervous system," etc., since it is an essential feature of their metabolism—that which renders all tissues susceptible to adequate oxidation, the underlying factor of normal development and function. The "transformation under the influence of the ferment in the thyroid" is naught else than the above process carried out, we have seen, under the influence of a ferment and the organic iodine, *i.e.*, by what I have termed "thyroidase." As to its rôle as "antitoxin," we shall now see that it is also a feature of the same process.

Youchetchenko credits Marbé, Malvoz, Fassin, and Stépanoff (the first- and last- named investigators being of the Pasteur Institute) with the credit of having first connected the thyro-parathyroid secretion with the modern conception of immunity, which takes into account the presence of alexins, opsonin, etc.,

⁷⁸ Youchetchenko: *Loc. cit.*, Tome xv, Nos. 3 and 4, 1910.

in the blood; but this is an oversight which Léopold-Lévi and H. de Rothschild, of Paris, corrected in their recent work⁷⁹ when they wrote: "Sajous has attributed to the secretion of the thyroid gland an action which he deems similar to that of the opsonins and to autoantitoxins. More recently, Miss Fassin, M. Stépanoff, M. Marbé have confirmed on their side the influence of the thyroid on the blood's asset in alexins and opsonins. All these researches explain the mechanism of everyday infections."

That I am entitled to the priority of this discovery will be shown presently in the course of the evidence in support of my contention, advanced several years ago,⁸⁰ that

The thyroparathyroid secretion increases the germicidal and antitoxic power of the blood by endowing the albuminous portion of the hæmoglobin with sensitizing properties. As such, it is the blood constituent Sir A. E. Wright has termed "opsonin."

Bordet's sensitizing substance, or "sensibilisatrice," was thought by this investigator and also by von Dugern to appear in the blood under the influence of the red corpuscles. Nolf⁸¹ showed, however, that it is owing to an action of the alexins or complement upon these cells that "the contents of the latter" are caused to leave them; he found also that "the injection of the corpuscular contents incites hæmolysis." Now, Savtchenko⁸² has pointed out that the "sensibilisatrice" is endowed with specific opsonic properties, acting both on bacteria and leucocytes—the identical sensitizing action discovered by Denys and Leclef⁸³ in 1895, and which Sir A. E. Wright has since studied with such promising results. Suggestive in this connection is Nolf's statement in reference to the production of antibodies that "it is solely to the injected red corpuscles that the power to bring forth these new substances must be attributed." When this is coupled with Barratt's⁸⁴ observation that opsonins "are also produced by injecting red blood-cells in the peritoneal cavity" of experimental animals, and also Briscoe's⁸⁵ to the effect that opsonin is present

⁷⁹ Léopold-Lévi and Rothschild: "Physio-pathology of the Thyroid Body." etc., 1911.

⁸⁰ Sajous: See vol. I, 1st ed., p. 762, 1903, and vol. II, p. 1093, 1907.

⁸¹ Nolf: Annales de l'Institut Pasteur, xiv, pp. 297 and 492, 1900.

⁸² Savtchenko: *Ibid.*, xvi, p. 106, 1902.

⁸³ Denys and Leclef: "La Cellule," xi, p. 198, 1895.

⁸⁴ Barratt: Proc. Royal Soc. of London, lxxvi, p. 534, 1905.

⁸⁵ Briscoe: London Lancet, Sept. 7, 1907.

in the fluid of the peritoneal cavity, which normally contains no phagocytes, it becomes evident that opsonin is a product of the red corpuscles.

Under these conditions, however, the administration of thyroid preparations should increase the immunizing properties of the blood, and particularly its opsonic activity. As to the former, I was led to conclude, in 1903,⁸⁶ by an analysis of the whole question, that the injection of various bacterial toxins in man and in the lower animals excited more or less actively according to their virulence the pituitary, adrenals, and thyroid (constituting what, as we shall see in another chapter, I termed the "adrenal system"), and that "the various antitoxic sera are more or less active in proportion as to the quantity of thyroiodine in them is great." Four years later, Miss Fassin⁸⁷ found not only that removal of the thyroid decreased the germicidal and hæmolytic alexins in the blood; but that the administration of thyroid by any method increased materially these same alexins. That this actually increases the defensive power of the body was also noted by Reid Hunt,⁸⁸ who found that when mice were fed on small amounts of thyroid they showed marked resistance to poisoning by acetonitrile. Ever since the gland has been used as a therapeutic agent, in fact, it has been found useful, though empirically, in intoxications of various kinds. Léopold-Lévi and de Rothschild,⁸⁹ for example, observed clinically that thyroid treatment rapidly influenced favorably autointoxications and exogenous infections, including erysipelas. Turró⁹⁰ found that the juices of swine and sheep thyroids dissolved almost entirely the comma, typhoid, and anthrax bacilli, the bacillus coli communis, and the streptococcus. Conversely, dogs were found by Charrin⁹¹ to succumb readily to infections, after removal of the thyroid. That toxic intermediate wastes or other toxics are not destroyed adequately in thyroidectomized animals is shown by the observation of Gley⁹² that the blood-serum of thyroidectomized dogs is more toxic than normal serum, and gives rise to convulsions when injected into animals. Jeandelize and

⁸⁶ Sajous: See vol. 1, 1st ed., p. 762, 1903.

⁸⁷ Fassin: C. r. de la Soc. de biol., Mar. 9 and 26 and Apr. 20, 1907.

⁸⁸ Hunt: Jour. Amer. Med. Assoc., July 20, 1907.

⁸⁹ Léopold-Lévi and de Rothschild: *Loc. cit.*

⁹⁰ Turró: C. r. de la Soc. de biol., ix, p. 464, 1906.

⁹¹ Charrin: Les Défenses Naturelles de l'Organisme, Paris, 1898.

⁹² Gley: Archives de Physiologie, No. 4, p. 770, 1895.

Perrin⁹³ also found that thyroidectomized rabbits presented less resistance to poisoning by sodium arsenas than normal animals. Lorand observed the same fact in connection with chloroform narcosis. De Luca and d'Angerio⁹⁴ and others have found, moreover, that the urine in thyroidectomized animals contains a greater percentage of toxic substances than normal, and that the therapeutic use of thyroid in these animals counteracted this toxicity. It is thus apparent that the evidence from every phase of the question points to the thyroid secretion as an important factor in the immunizing processes of the body.

The process through which the thyroparathyroid secretion carries on this important function differs in no way from that which enables it to sustain metabolism and nutrition. As stated by Jordan:⁹⁵ "The bodies of bacteria contain from about 80 to 88 per cent. of water, the amount showing considerable variation and depending partly on the nature of the organism, partly of the culture-medium. The ash is *largely phosphoric acid*, the P_2O_5 often reaching as high as half the total ash weight (tubercle bacillus, 55.23 per cent.; de Schweinitz and Dorsett⁹⁶)." Bacteria, therefore, in keeping with many of our tissue-cells, are relatively rich in phosphorus and correspondingly vulnerable to the action of the thyroiodase. As the latter, in turn, renders the phosphorus prone to oxidation by the plasmatic adrenoxidase, the whole pathogenic micro-organism is rendered unstable chemically and vulnerable to the digestive influence of the blood's germicidal agents—which in the above sense include both the thyroparathyroid and adrenal products acting conjointly.

On the whole, the evidence and the confirmatory testimony submitted under the last two headings have shown:—

1. *The thyroparathyroid secretion and the thyroid preparations used therapeutically act by increasing the sensitiveness of the phosphorus of all cells, particularly their nuclei, to the oxidizing action of the adrenoxidase, and thus enhance metabolism and nutrition.*

2. *They also, in virtue of this action, augment the auto-protective, or immunizing, power of the blood, by increasing the*

⁹³ Jeandellze and Perrin: Réunion biol. de Nancy; cited by Parhon and Golstein, *loc. cit.*, p. 554, 1909.

⁹⁴ De Luca and d'Angerio: *Revista medica e terapeutica*, No. 9, 1896.

⁹⁵ Jordan: "General Biology," 2d ed., p. 67, 1910.

⁹⁶ De Schweinitz and Dorsett: *Centralbl. f. Bakt.*, Bd. 22, S. 209, 1897.

sensitiveness (as opsonin) of all bacteria, their toxins, endotoxins, toxic wastes, etc., that contain phosphorus to oxidation, and thereby to the digestive or destructive action of the complement, both in the blood and in its phagocytes.

As will be shown elsewhere in this work, this represents the foundation (with the adrenal and pancreatic secretions as additional factors) of the autoprotective process, including the germicidal cytase of phagocytic cells. It traces them to their origin and furnishes their identity, features which Ehrlich's labors have not, so far, determined.

THE PITUITARY BODY AS THE SEAT OF THYROPARATHYROID CENTER.

So important are the functions of the thyroparathyroid apparatus that we cannot but surmise that, in keeping with many other and far less prominent functions, they are regulated by a center. The evidence available, a part of which is given below, and in the second volume, indicates that such is the case.

That it should be the same center which we have seen governs the functions of the adrenals is not only sustained by what evidence there is on the subject, but also by logical reasoning, since the two centers which regulate oxygenation, metabolism, and nutrition, thus conjoined, are placed in the most advantageous position to co-ordinate these all-important functions.

The first clue to such a functional relationship was afforded by the fact that

The active and passive phenomena evoked by the pituitary body and the thyroid apparatus show considerable parallelism.

We have seen that removal of either the pituitary or the thyroid causes a steady decline of the temperature with decreased oxygen intake and carbon dioxide output, and also weakness, tetany, and even epileptic convulsions, while, conversely, overactivity of either organ provokes excessive metabolism with increase of oxygen intake and carbon dioxide output, and glycosuria. We arrest nutrition by removing either the pituitary or the thyroid, just as degenerative changes in either organ entails denutrition lapsing into fatal cachexia. The sthenic stage of acromegaly and gigantism strikingly illustrates the power of the pituitary to incite excessive nutrition and over-

growth; the rapid growth of the cretin under the influence of thyroid preparations exemplifies what the thyroid apparatus can do in the same direction.

The simultaneous presence of degeneration of the pituitary and myxœdema in cases reported by Ponfick,⁹⁷ J. Stewart, Codd,⁹⁸ Sainton and Rathery,⁹⁹ and others; and of acromegaly with exophthalmic goiter by Murray,¹⁰⁰ Lancereaux,¹⁰¹ and others (two diseases which, as emphasized by Lorand, not only present many characteristics in common, but which, as observed by Magnus-Levy,¹⁰² are attended by excessive oxidation) clearly suggest functional parallelism. This is further emphasized by the enlargement of both organs during pregnancy indicated by the labors of Comte,¹⁰³ Launois and Mulon,¹⁰⁴ and Lang¹⁰⁵ and its subsidence when, after parturition, the blood no longer receives the excess of wastes that the presence of the foetus involved. On the whole, we can certainly say with Thaon¹⁰⁶ that "between the pituitary and the thyroid there is so much analogy that the one cannot be studied without a knowledge of the other."

Zoölogy affords various landmarks in the same direction.

The pituitary body governs oxygination, metabolism, and nutrition in all animals supplied with a thyroid gland and adrenals.

In tunicata, the homologue of the thyroid, according to zoölogists, is the endostyle, a long gland at the base of the pharynx closely related to the branchial or respiratory chambers. The adrenals in these invertebrates are represented, as personal researches have suggested, by the dorsal tubercle, which is so related to the respiratory chamber that its product, which corresponds with the adrenal secretion, can be secreted into the blood near the oral aperture, the inlet for the water which supplies the animal with oxygen. Suggestive in the light of the views I have submitted is that the dorsal tubercle—the primitive organ of the adrenals from my viewpoint—is connected by a

⁹⁷ Ponfick: Zeit. f. klin. Med., xxxviii, Nos. 1, 2, u. 3, 1900.

⁹⁸ Codd: British Medical Journal, May 5, 1895.

⁹⁹ Sainton and Rathery: C. r. de la Soc. méd. des hôpitaux, May, 1908.

¹⁰⁰ Murray: Edinburgh Medical Journal, February, 1897.

¹⁰¹ Lancereaux: La Semaine médicale, June 24, 1896.

¹⁰² Magnus-Levy: British Medical Journal, April 3, 1903.

¹⁰³ Comte: Thèse de Lausanne, 1898.

¹⁰⁴ Launois and Mulon: Ann. de gynec. et d'obstét., 2d series, 1, p. 2, 1904.

¹⁰⁵ Lang: Zeit. f. Geburts. u. Gynäk., xl, p. 34, 1889.

¹⁰⁶ Thaon: Loc. cit., p. 116.

delicate duct with an organ, the subneural gland, which Julin, as we shall see presently, has identified as the hypophysis, while the endostyle, the primitive thyroid, along with all other organs, receives nerve-fibers from a nerve-ganglion attached to this ancestral pituitary.

Two important facts impose themselves in this connection: The first is that, as stated by Jacques Loeb¹⁰⁷ in reference to a group of these invertebrates, "the central nervous system is reduced to a single ganglion"; the second is that this single ganglion corresponds with the neural or posterior lobe of the pituitary. Just as the nerve-ganglion governs the functions of the primitive thyroid and adrenals, that is to say, the respiratory processes in these lowly animals, so can it be shown to do at every step of the phylogenetic scale up to man, since it preserves its functional importance throughout. The snail, for example, is supplied with both a cerebral and an œsophageal ganglion; galvanic excitation of the cerebral ganglion, as shown by Vulpian, produces no appreciable effect; but similar excitation of the lower or pharyngeal ganglion, the future neural lobe of the pituitary, provokes violent muscular movements. Again, removal of the cerebral ganglion will not kill the animal, but it will remain motionless. Extirpation of the œsophageal ganglion, on the other hand, causes its death in less than twenty-four hours. All this applies as well to other invertebrates.

We can assimilate all the vertebrates to these primitive forms by removing the brain. That the respiratory mechanism or the processes it influences are not in the least impaired by this operation was shown when we traced the governing centers of this mechanism—to which the thyroid belongs—to the pituitary. The well-known Cornell frog lived several years after its brain had been removed. The decerebrated pigeon is a familiar example of this kind. Another is Goltz's dog which lived eighteen months after both its hemispheres had been removed. Conversely, we have seen how rapidly extirpation of the pituitary proves fatal in the higher mammals, just as it does in the low invertebrates when the œsophageal ganglion is extirpated. We found that all the lethal phenomena are due to arrest of respiration and oxidation, both of which processes are carried on through the adrenals and the thyroids. Again,

¹⁰⁷ Jacques Loeb: "Studies in General Physiology," part 1, p. 363, 1905.

In vertebrates the pituitary body is connected with the thyroparathyroid apparatus, as it is with the adrenals, by direct nerve-paths.

The thyroid apparatus, as all textbooks teach, receives its nerves from the sympathetic through the middle and inferior cervical ganglia. That they originate in the pituitary is shown not only by the presence of typical sympathetic fibers between the pituitary and the upper connections of the spinal system with the cervical sympathetic, but also by the effects of electrical excitation of the exposed, but normal pituitary.

As to the origin of the nerves, Cajal,¹⁰⁸ Joris,¹⁰⁹ and others, we have seen, traced in various animals fibers from the pituitary to a nucleus of large gray cells immediately above the infundibulum in the anterior portion of the third ventricle, which nucleus was found by them to project nerves over the ventricular walls. These nerves are also described by Edinger¹¹⁰ in fishes, reptiles, and birds as "numerous fine, medullated fibers"—the characteristics of sympathetic nerves, as shown by Bidder and Volkmann. In illustrations of sections in various animals, Edinger shows, moreover, that several bundles of these fibers project posteriorly as far as the level of the bulb, whence, as is well known, the fibers which pass over to the sympathetic ganglia begin to leave the spinal system. As the ganglia are the starting points of sympathetic nerves to the various organs, we thus have, through these ganglia, a continuous path from the pituitary to these organs. This is sustained by physiology, since C'yon and also Masay¹¹¹ caused an instantaneous rise of pressure of over 100 mm. Hg. by exciting electrically the exposed pituitary. As the vagi were cut during the experiment, and the vasomotor center is independent and located in the bulb, the rise of pressure could only be due to general sympathetic vasoconstriction. I will show in the second volume that the pituitary has a controlling power over the sympathetic system.

When the influence of the pituitary over the adrenals was analyzed, it was possible to trace step by step along the path

¹⁰⁸ Cajal: *Loc. cit.*

¹⁰⁹ Joris: *Loc. cit.*

¹¹⁰ Edinger: "Anatomy of the Central Nervous System," American edition, p. 260, 1899.

¹¹¹ Masay: *Ann. de la Soc. roy. des sci. méd. et nat. de Bruxelles*, xli, part ii, 1903.

between the two organs all the main phenomena which both were able to provoke. In the case of the thyroid we are deprived of this valuable testimony. As Morat,¹¹² in his review of the sympathetic system, says, "the thyroid gland receives its vasomotor fibers from the superior portion of the thoracic chain by the cervical cord. Stimulation of the thoracic chain causes either vasoconstriction or vasodilatation on account of the mixture of the two orders of fibers." In other words, the antagonistic nerves which control the functions of the thyroid are so conjoined that transection or excitation would afford no reliable testimony.

The participation of the thyroid in the phenomena awakened by the pituitary and the nerves it projects posteriorly is shown, however, by the intensity of these phenomena. The adrenal secretion alone, as represented by its extracts, causes a rise of temperature of 1° or 2° F. How account for the rise of 10° F. and over caused by puncture of the tuber cinereum (just above the pituitary) by Sakowitsch¹¹³; of the 6° F. and over noted by Brück and Günther¹¹⁴ on puncturing between the pons and medulla, and of the 12.4° F. noted by Brodie¹¹⁵ after an injury of the cervical portion of the spinal cord, with impulses to the adrenals alone to account for these heat phenomena? They obviously fail to do so. On the other hand, they are readily explained by *simultaneous* impulses to the thyroid apparatus, since the action of its secretion upon cellular phosphorus, we have seen, provides an active source of heat energy. This dual action not only accounts for the high temperatures obtained by irritation applied all along the path from the pituitary down to where the nerves to the adrenals and thyroid leave the spinal cord, but it indicates that the two sets of thermogenic nerves follow the same path, down to this region.

Finally, that the pituitary is so related with the nervous system as to be capable of governing these organs, is further shown by the fact that, as stated by Prof. Laulanić,¹¹⁶ a physiologist who has given considerable attention to the functions of the ductless glands, in reference to the pituitary body, "this gland

¹¹² Morat: "Physiology of the Nervous System," Syers's ed., p. 334, 1906.

¹¹³ Sakowitsch: *Loc. cit.*

¹¹⁴ Brück and Günther: *Loc. cit.*

¹¹⁵ Brodie, Morat, and Doyon: *Loc. cit.*, Article Calorification, p. 413, 1899.

¹¹⁶ Laulanić: "Éléments de Physiologie," 2d ed., p. 488, 1905.

is, in fact, in relation with the sympathetic, the vagus, and the depressor nerve."

Of course, I am familiar with the prevailing view that the pituitary is a secreting gland. But the data which tend to sustain this opinion are far from convincing, for reasons that I will submit in the tenth chapter. Suggestive in this connection is the fact that its removal for tumors or other lesions which destroy its functions does not in the least compromise life, as is the case after removal of the adrenals or of the thyroparathyroid, which are known to be secreting glands. Were the pituitary the source of any such secretion, its extirpation would obviously provoke serious disturbances. With this organ interpreted in accord with my views, *i.e.*, as a co-ordinating center acting through subsidiary centers in the bulb capable of assuming its functions increasingly as these are being annulled by the pituitary lesion, absence of postoperative complications is explained.

Again, the main evidence of those who believe in the existence of an internal secretion is based on the rise of the blood-pressure observed after injections of pituitary extract. "According to Kohn,"¹⁷³ writes Swale Vincent in his recent work,¹⁷⁴ "there is nothing to suggest that the posterior lobe has an internal secretion, in spite of all the results of experiments involving the injection of extracts." . . . "We have seen that the extracts having powerful effect upon the blood-pressure and the flow of urine are obtained from the posterior lobe and not from the epithelial layer which covers it. This view seems to be borne out by the experiments of Franchini. Now, the posterior lobe proper (excluding the epithelial layer) consists of neuroglia, pigment, and occasional nerve-cells." Swale Vincent then aptly remarks: "It is extremely difficult to imagine how such a structure can be regarded as a secreting gland."

Pending additional evidence to this effect, and referring the reader to preceding chapter for testimony concerning the connection between the pituitary and the adrenals, the conclusion is submitted that

The pituitary body contains the governing center of the parathyroid apparatus and adrenals, and co-ordinates the secretory activity of these organs.

¹⁷³ Kohn: Münch. med. Woch., Nu. 28, 1910.

¹⁷⁴ Swale Vincent: "Internal Secretion and the Ductless Glands," p. 401, 1913.

CHAPTER IV.

DISEASES OF THE THYROPARATHYROID APPARATUS.

DISORDERS DUE TO DEFICIENT ACTIVITY OF THE THYROPARATHYROID APPARATUS.

IN the light of the data and conclusions submitted in the preceding chapter, the phenomena awakened by functional disorders of any kind in the parathyroid apparatus should be of two kinds: those due to excessive functional activity now known as "hyperthyroidism," and those due to inadequate functional activity, and designated as "hypothyroidism." A third class, termed by Léopold-Lévi and Rothschild "thyroid instability," introduces both the former types, but either in alternation or concomitantly in the same subject. In the present chapter we shall consider the first type, viz., that in which, as stated in the above heading, the functions of the thyroparathyroid apparatus are inadequate, in that the secretion it supplies the organism is insufficient to carry on normally the functions described in the foregoing pages.

The classification of the disorders due to deficient activity of the thyroid apparatus being in its formative stage, so to say, many expressions and terms have been introduced, such as "thyroid insufficiency" or "inadequacy"; "hypothyroidism," or "attenuated," "benign," "incomplete myxœdema"; "myxœdeme fruste," and others, to denote the milder forms of this disorder; and quite as many others to designate the severe forms considered in the next chapter. None of these terms seem to me to interpret satisfactorily the morbid process in question. Restricting ourselves for the moment to the milder forms, such terms as "thyroid insufficiency" or "inadequacy" are too cumbersome; "hypothyroidism" implies the presence of a habit such as "alcoholism"; "incomplete myxœdema" and "myxœdeme fruste" are not applicable in most instances of this disorder, since no myxœdema of the skin, mucous membranes, etc., is discernible.

Worst of all is the term "athyrea," which perverts the name of the gland, "thyro-" or "thyroid" being necessary in composition to indicate a connection with the "shield-like cartilage." It has appeared to me, therefore, that the simplest term would fill our needs best, until the many morbid states and syndromes it covers will have been, to say the least, more accurately identified. Of all the terms available is that adapted from the French "hypothyroïdique," *i.e.*, *hypothyroidia*, which also presents the advantage of corresponding as to its terminal with anemia, hyperchlorhydria, and many other terms in current use.

As to the pathogenesis of this condition, it must also be said that at the present time little or no effort is made by writers to explain the manner in which thyroid insufficiency brings about each of its characteristic symptoms. The functions I have attributed to the thyroid and to the adrenals in the preceding chapters enable us to do otherwise. In the present connection, therefore, it is essential to recall that, with these functions in abeyance or depressed, we shall have to deal with three essential morbid factors:—

1. Deficient tissue oxidation, the rate of metabolism and nutrition in all tissues, particularly those rich in phosphorus, such as the nervous system, cellular nuclei, etc., being retarded.

2. Deficient breaking down of waste products, fats, etc. (slowed metabolism entailing deficient catabolism), with accumulation of fat, detritus, wastes, etc., in the blood and tissues as a result.

3. Deficient resistance of the body to infection and intoxication, owing to insufficient production of opsonin (the thyro-parathyroid secretion) and of the other antitoxic and germicidal blood constituents and phagocytic cells, as a result of the slowed metabolism in all organs producing them.

HYPOTHYROIDIA.

(Chronic Benign Hypothyroidia; Hypothyroidism; Incomplete Myxœdema; Myxœdème Fruste.)

The term "hypothyroidia" is intended to include all conditions of the organism that are due to deficiency of the thyro-parathyroid secretion, but not the advanced types of this condition, such as myxœdema and cretinism, which are reviewed

farther on. It includes the so-called "incomplete" form, and, as such, is far more important clinically than even myxœdema, since, as we shall see, it forms part of, or complicates pathogenically, many diseases that we meet almost daily in practice.

The history of hypothyroidia is linked with that of its more severe form, myxœdema. The results of surgical removal of the thyroid by the brothers Reverdin were reviewed early in the preceding chapter. The medical side of the question, as regards the milder form with which we are now concerned, was first described by J. L. Reverdin,¹ one of the two brothers referred to above, in 1887, who gave it the name of *myxœdème fruste*. Valuable articles on the subject were then contributed by Thibierge,² Chantemesse and Marie,³ Murray⁴ and Brissaud,⁵ and others, in which many cases were reported, but that of Hertoghe,⁶ of Antwerp, in which he termed the disorder "chronic benign hypothyroidia" is worthy of special attention owing to the multiplicity of clinical features introduced and the accuracy of the author's conclusions.

While many symptoms of hypothyroidia are witnessed in myxœdema, the latter in its typical form is a comparatively rare disease. The former is also thought to be infrequent, but this is merely because it generally passes unrecognized. This is mainly due to its classic association with the frank type of myxœdema, which leads the clinician to seek for the most salient symptoms, *e.g.*, cutaneous myxœdema, dry skin, the mask-like face, etc. Not finding these phenomena he transfers his analysis of the case to other possible morbid processes. In truth, the symptom-complex of hypothyroidia does not, in the great majority of cases, include the prominent symptoms of myxœdema. Moreover, while the latter disease is progressive when left untreated by modern methods, hypothyroidia is not; but it keeps the patient in a state of perpetual torment. The physician, failing to recognize the true identity of the trouble, leaves the patient a prey to acute suffering from so-called rheumatism, neuralgia,

¹ Reverdin: *Revue méd. de la Suisse Romande*, vol. vii, p. 275, 1887.

² Thibierge: *Gazette des hôpitaux*, vol. lxiv, p. 117, 1891.

³ Chantemesse and Marie: *Bull. et mém. de la Soc. méd. des hôpitaux de Paris*, vol. xi, p. 124, 1894.

⁴ Murray: *British Medical Journal*, Oct. 1, 1898.

⁵ Brissaud: "*Nouv. iconographie de la Salpêtrière*," p. 240, 1897.

⁶ Hertoghe: *Ibid.*, p. 261, 1898.

tic douloureux, sciatica, etc. The sufferer finally abandons treatment—at least that offered by medical men.

Another perhaps still broader field in which the recognition of hypothyroidia is of great practical importance is the process of development, physical and mental, of the child. We have sufficient evidence of the effects of athyroidia (complete deficiency of normal thyroparathyroid secretion) in cretinism, *i.e.*, infantile myxœdema. That a reduction of the same secretion should compromise correspondingly the physical and mental welfare of a child without necessarily branding it with the physical signs of cretinism is an established, though little recognized, fact. Indeed, a large proportion of backward children and the oft-punished laggards of the class-room are but sufferers of hypothyroidia.

Finally, certain diseases, syphilis, tuberculosis, and other infections, and also certain abuses of the physical powers, such as multiple pregnancies, prolonged lactation, excessive venery, or masturbation, so weaken the thyroparathyroid apparatus and the adrenals, with which it is, we have seen, intimately linked functionally, that hypothyroidia results. The recognition of this condition as an underlying factor means not only a marked development of our diagnostic resources, but it affords also opportunities for successful therapeutics where, before, failure was the rule.

A definition which appears to me to facilitate the recognition of this disease is the following:—

Hypothyroidia is a constitutional disease due to deficient functional activity of the thyroparathyroid apparatus, when the secretory activity of the latter is not sufficiently impaired to give rise to the most advanced and progressive type of the disease: myxœdema. The symptoms of hypothyroidia most frequently met with, separately or unitedly, are: severe occipital and interscapular pain, obesity with supraclavicular fat pads, hypothermia, loss of hair and teeth, lassitude, stubborn constipation, and mental torpor, supplemented in children by slow physical, mental, and irregular skeletal development, enlargement of the lymphatic glands, and, occasionally, enuresis.

SYMPTOMATOLOGY.—The symptomatology of hypothyroidia includes many of the symptoms of the asthenic disorders of

nutrition, but, as there exist many gradations of this condition, hypothyroidia representing as many degrees of thyroparathyroid secretory activity, its symptoms are more or less prominent both in number and intensity.

These patients usually apply for relief of pain of some kind, particularly pain in the back or in the occipital region, and occasionally for migraine or neuralgia. The "backache" may consist of sacrolumbar pains, of coccygodynia, or in most instances of very severe deep-seated pain between the shoulder-blades, which rest in bed tends to aggravate rather than to improve. These phenomena are due to deficient catabolic activity, the blood being laden with toxic products—a known cause of such symptoms. That rest in bed should aggravate the condition is self-evident: it merely slows still more the oxidation process and thereby encourages the catabolic torpor. They complain of feeling fatigued, languid, somnolent on rising, and of being in every way worse; while, as the day wears on, their condition improves. Their temperature is low, and they complain of always feeling cold, especially at the extremities. Their hands are flabby, damp, though cold chills may even be complained of. We have here an evidence of the slow metabolic activity referred to above, every sign of deficient oxidation being present. This explains also why a copious meal, especially if it includes the use of alcoholic beverages, should be a source of great relief in these cases, and why, also, they readily become addicted to the immoderate use of alcohol as a "stimulant."

A close examination then reveals other morbid phenomena which are obviously due to the defective nutrition of all tissues which hypothyroidia entails. The patient appears much older than her age—women constituting a large proportion of these cases. The hair may be prematurely gray, showing a marked tendency to fall in patches from the forehead and median line, which tends to become wider, and from the occiput. This loss, which is attributed by the patient to the headaches, may be such as eventually to cause complete alopecia. In marked cases the hair may be coarse, dry, and brittle, as in the cretin. The eyebrows also show a tendency to fall, but, a characteristic sign of hypothyroidia: the loss is limited to the external or outer ends. This shortening of the eyebrows and the occipital loss of hair

denote, jointly, rather marked cases, though the shortened eyebrows are frequently met in the less severe. In the former, the skin of the face may also appear infiltrated and be hard to the touch, as in myxœdema, its color being waxy, with perhaps a reddish patch below each cheek-bone. Although the skin of the body may be normal, that of the legs, especially below the knees, usually feels rough, rasp-like, and may be scaly, the scales, which are readily detached, recalling dandruff, which is also present in most cases. Pads of fat especially prominent over the clavicle seem characteristic of rather marked cases. Such symptoms, which belong to true myxœdema, are rarely observed, however, though a waxy hue of the facial skin and puffy lids are not uncommon.

Dyspnoea or oppression, due to deficient oxygenation of the blood, is complained of on climbing stairs or during continued speaking. Palpitations, sometimes of a distressing character and with severe pain, may also occur. The heart is often found dilated with weak systole and occasional murmurs. The blood-pressure is low, from 80 to 110 mm. Hg., and the pulse weak and rapid. All these symptoms are directly traceable to the existing impairment of the oxidation and nutrition, the cardiac and vascular muscles suffering from this condition as well as all other organs. The blood-forming organs being also inadequately nourished, anemia is the rule, the erythrocytes being usually reduced to about 3,000,000, with more or less anisocytosis. Every type of cellular alteration seems to have been observed in this disorder, but, as a rule, what changes occur are not very marked. The hæmoglobin may be considerably reduced.

The teeth, especially the molars, tend to become loose and carious unduly early, owing to the deficient calcium and phosphorus metabolism which deficient thyro-parathyroid secretion entails, and need the constant attention of the dentist, who, as a rule, informs them that they are gouty—with "uric acid" as main cause of the dental trouble—not a misleading statement so far as the "gouty diathesis" is concerned, for it is closely linked also with hypothyroidia. The teeth are also exceedingly prone to become tartrous and require frequent cleansing. Where the teeth are neglected, as in the poor, they are rapidly lost, frequent toothache causing them to be drawn. The gums tend

to bleed readily when brushed and to recede from the teeth, and are red and swollen unless the toilet of the mouth be carefully attended to.

The deficiency of germicidal activity (phagocytic and humoral) manifesting itself where protection is usually quite active, *i.e.*, along mucous surfaces, the nasopharyngeal mucous membrane is also apt to be congested through the local accumulation of germs, the tonsils showing, for the same reason, a predilection to acute inflammation. The nasal mucosa is often found turgescient, owing to passive congestion of the underlying tissues. This gives the voice the nasal "twang," but it may also be husky or otherwise modified or veiled, through infiltration of the laryngeal mucosa. The singing voice tends to be false from the same cause, especially during the menstrual period. A "crick" in the larynx is commonly complained of.

Deficient metabolism and nutrition account for the general asthenia with lassitude and weakness of the knees, which is present in practically all cases. Fibrillary motions of the muscles and trembling occur in severe cases from the same cause. Constipation due to deficient peristalsis is also the rule, and it is often sufficiently obstinate to demand constant purgation—which tends to increase the intestinal torpor. Fecal impaction is not uncommon. The liver is passively congested and enlarged—a fact due to the low general vascular tension which explains also the presence of varicose veins, varicocele, and kindred vascular disorders frequently observed in these cases. They seem also to suffer frequently from biliary or renal calculi, a condition due mainly to deficient germicidal activity of the blood. The urine is often high-colored and scanty, and occasionally contains albumin, casts, sugar, or blood.

Flat-foot is sometimes observed, a condition due to relaxation of the interosseous muscular and ligamentous supports; foetid hyperidrosis is also marked in some cases. The osseous framework is often defective, "pigeon-breasts," narrow chests, and a predisposition to caries being common.

The organs of generation are often the seat of functional disorders. The uterus is often found retroflexed. Impotence or loss of sexual desire is common. Amenorrhœa is common, but metrorrhagia may also occur, owing to the low vascular tone,

particularly of the arterioles. In one of my cases, a girl of 16 years, there was what the parents termed "a constant leak," *i.e.*, a slight, but continuous menorrhagia. In the male, spermatorrhœa and prostatic hypertrophy are often witnessed. Menstruation sometimes fails to appear, especially in congenital cases, owing to inadequate development. The menstrual period is attended by severe lumbosacral pains. Pregnancy often affords considerable relief of all symptoms, owing to the fact that the activity of the thyroparathyroid apparatus is greatly enhanced, though it may be attended by hæmorrhages. Parturition is likewise accompanied by copious hæmorrhages in a larger proportion of cases; such parturients are exposed also to eclampsia, owing to imperfect catabolism of toxic wastes.

Lactation may act in different ways. The pallor tends to increase in some, and œdema, especially of the ankles, anæmia, lassitude, and intellectual torpor may intervene and last until the infant is weaned. As milk is mainly composed of blood-plasma containing adrenoxidase (as shown by the guaiac and other tests), lactation imposes increased activity upon the adrenals. These organs being weakened by the hypothyroidia, we have seen, all the above hæmorrhagic phenomena occur. In other cases there is marked improvement during the whole period, and the symptoms of hypothyroidia return only after the secretion of milk ceases. In occasional cases, the improvement is permanent.

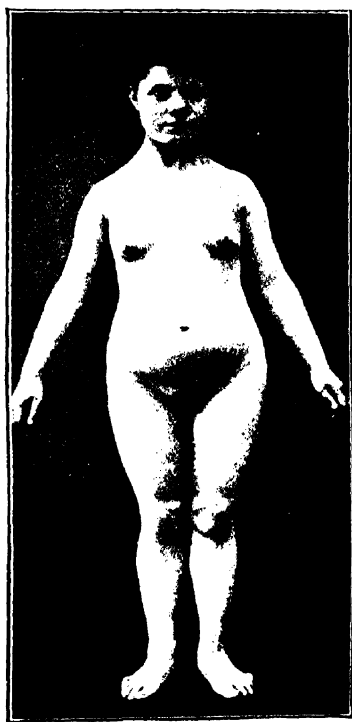
Hallucinations of sight—as of small animals running across the room—and hearing, rumbling noises or running water, and various forms of tinnitus may occur. These are due to the same loss of vascular tone, and imperfect circulation in the sensory organs.

Melancholia or, at least, an uncontrollable sadness, due to deficient nutrition of the cerebrum, is often witnessed in severe cases, especially during menopause. Maniacal excitement is occasionally observed, owing probably to accumulation of toxic wastes in the blood. The mind, even in the milder cases, is usually obtuse, in the sense that they lack *esprit*, *i.e.*, the ability to grasp the finer points of an argument or of a question treated in the abstract, but they are not in any way comparable to true myxœdematous subjects in this particular, some of whom ap-

proach closely the mental status of cretins. Like the latter, however, even average cases may have the arched brow and wrinkled forehead, the expressionless and sorrowful face, though to all intents and purposes of average commonplace intelligence. In most instances, however, none of these purely myxœdematous features can be discerned and a high grade of intelligence even exist, as in one of my cases, whose family—including a high-grade imbecile brother—and descendants show distinct traces of hypothyroidia.

The thyroid affords very little information under physical examination in these cases. One lobe may feel smaller than the other when, on the patient being asked to swallow, the organ is raised under the palpating fingers; the organ may seem unusually small, and the neck unusually flat; but again, it may appear enlarged. On the whole, the organic changes are not such in these cases as to alter sufficiently the outline of the organ to furnish any serious diagnostic aid.

Most authors refer to the disease as one of middle life, but this is an error. This type of hypothyroidia occurs frequently, we have seen, among children, and represents a large proportion of those termed "backward" in the schools, and among those accused of being "lazy," "slow," and "dull." This applies as well to adolescence, particularly, as in children, in those who are abnormally stout. All these cases may not present the syndrome just described; it is, in fact, rarely met with in any one case, but the superfluous fat, the mental torpor, the slow development, and the carious teeth are sufficient to indicate that the oxidations and metabolism are inadequate. The familiar influence of thyroid preparations on adiposis also points to hypothyroidia as the underlying cause of this condition. It may also assert its presence through a few phenomena of another order in a bright child, to-wit: irregular bony growth, a slight scoliosis perhaps, or true rachitis, flat feet, a narrow thorax, some pallor, hypothermia, undue vulnerability to infection, or one or more of the many other symptoms described above. Some, on reaching the fourth or fifth decade—particularly women approaching or undergoing the menopause—begin to show typical symptoms and soon lapse into full-fledged cases—recalling that several of the symptoms now revealed as part of complete syndrome, sensitive-



HYPOTHYROIDISM. [*Appl. Med. & Surg.*, 1907, 12]

Physical development under thyroid treatment.

ness to cold, neuralgia, anæmia, menorrhagia, etc., had been present many years.

ETIOLOGY AND PATHOLOGY.—The causes of hypothyroidia may be divided into two classes, the hereditary and acquired.

The most important *hereditary* causes which entail defective development, morphological and secretory, are syphilis, alcoholism and the gouty diathesis. Even far back in the parental lines on either side, these transmit their influence through the intermediary of the ductless glands, especially the thyroid, adrenals, and pituitary body, which, jointly, in the light of the data submitted, carry on oxidation and metabolism and thus constitute, so to say, the tripod of the vital process. The maternal line is generally thought to transmit hypothyroidia in the majority of instances. It happens that some of the most marked cases I have had were clearly traceable only through the paternal ancestry—three generations in one instance. Consanguinity in marriage probably owes its evil effects to the presence in the family of one of the deteriorating diseases mentioned. Conversely, marriage of a girl suffering from a mild type of functional hypothyroidia sometimes brings on recovery if pregnancy occurs, the increased activity of the thyroid apparatus this entails causing it to develop its functional powers to the maximum needs of the subject. That the adrenals are also overactive under these conditions—thus sustaining from another direction my view that the adrenals are stimulated by, and concomitantly with, the thyroid—was recently emphasized by the observation of Neu,⁷ who found an excess of the adrenal product in the blood throughout the entire period of gestation.

The *acquired* form is often due to the identical factor just referred to as a curative one in some instances. The repetition of pregnancy too many times may not only cause recurrence of hypothyroidia by exhausting the thyroid apparatus, but it may likewise do so in a woman previously free of any disorder of the ductless glands. Prolonged lactation acts in a similar way, the maternal milk serving, we have seen, to protect the nursling against infection. Infectious diseases, especially those of childhood, including the milder ones, measles and mumps, and likewise variola and typhoid, may also produce hypothyroidia by

⁷ Neu: *Medizinische Klinik*, Nov. 3, 1910.

causing interstitial and parenchymatous lesions which lead to sclerosis and atrophy. The resulting phenomena are proportionate, of course, with the degree to which the functions of the thyroid are inhibited. These may occur in the midst of the disease, the child failing thereafter to grow physically and mentally at the normal rate and becoming flabby and pale, and showing the typical symptoms of functional hypothyroidia—if not its more advanced stage, cretinoid infantilism. Traumatism of the thyroid may also produce it. Amenorrhea, as noted by Macfarlane^{7a} may be the salient symptom of the disorder.

Old age stands apart perhaps from these two classes in that it is normal to all living things; but the thyroid apparatus stands pre-eminently, we have seen, as the underlying factor in this connection, according to Lorand,⁸ who traces the cause of senility back to the thyroid, Victor Horsley, Hale White,⁹ Erdheim, and others having found this organ atrophied, and containing connective tissue, in aged subjects. This was found to occur as early as the fiftieth year in the seventy thyroids examined by White. As noted by Erdheim, the same evidences of degeneration appear in the parathyroids. I look upon concomitant changes in all the organs of the adrenal system, the thyroid, adrenals, and pituitary, as the underlying cause of senility.

The symptomatology of senility and that of atrophy of the thyroid gland present considerable resemblance, as Léopold-Lévi¹⁰ holds to hypothyroidia; the wrinkled, dry skin, the sub-normal temperature, the alopecia, the thinning of the eyebrows, the loss of teeth, the anorexia and constipation, the diurnal somnolence, the suppression of the menses and of the sexual function, the vague muscular pains, the enfeeblement of all functions, and the tendency to degeneration, particularly of the vessels, being common to both conditions.

TREATMENT.—Small doses of thyroid cause gradual disappearance of the morbid phenomena, while large doses may aggravate them. As emphasized by Hertoghe, the actual secretory activity of the thyroid apparatus is an unknown quantity, and large doses, by suddenly bringing on headache, pain over the

^{7a} Macfarlane: *Jour. of the Am. Med. Assoc.*, Feb. 3, 1912.

⁸ Lorand: "Old Age Deferred," p. 91, 1910.

⁹ White: *Med. Chirur. Trans.*, vol. lxxi, p. 182.

¹⁰ Léopold-Lévi: *Jour. de méd. de Paris*, No. 26, 1909.

kidneys, articular, muscular, and hepatic pains and anorexia—to which I would add a rapid pulse, fever, a tendency to faint, tremors, and increase of the existing dyspnoea—merely serve to frighten the patient and cause unjustified condemnation of the treatment. The treatment should be persisted in for years if need be, as emphasized by a case reported by G. E. Price.^{10a}

One grain of the desiccated thyroid gland during meals is sufficient to begin with in an adult. This may be gradually increased until 2-grain (0.132 Gm.) doses are given. Patients seldom stand larger doses well, and these are only warranted when the prolonged use of the smaller fails to improve the patient. Often when improvement is not noticed the fault lies with the preparation administered; a change should then be made. In mild cases one-half of the above doses often suffice.

When the anæmia is profound, the effects of treatment are enhanced by giving desiccated adrenal gland, 2 grains (0.132 Gm.), and a small dose of iron, 1 grain (0.066 Gm.) of Bland's pill, with each dose of thyroid. Such a small dose of iron does not increase constipation, and contributes to the rapid building up of the hæmoglobin molecule. The three agents can be given in a capsule. The constipation should receive careful attention. High injections of saline solution two or three times a week are sometimes necessary in severe cases to evacuate completely the lower bowel. This measure may be resorted to the first three or four weeks if needed, and replaced by glycerin suppositories until a free motion occurs daily. Usually the fourth week of thyroid treatment is attended by considerable progress in this and all other directions. Saline aperients are to be preferred if purgation *per ora* becomes necessary. Opiates are harmful.

MYXŒDEMA, OR PROGRESSIVE HYPOTHYROIDIA.

In this disease we have the maximum expression of progressive hypothyroidia, as it develops after the process of body growth has been accomplished, *i.e.*, in the adult. When the corresponding disorder occurs during childhood or adolescence, it stunts growth of body and mind and is then known as cretinism, treated under the next heading.

¹⁰ G. E. Price: *American Medicine*, Aug., 1911.

The marked inhibition of the thyroparathyroid functions that characterizes this disease is graphically illustrated in its symptomatology when these functions are interpreted from my viewpoint. The great diminution of the thyroparathyroid secretion correspondingly impairs the sensibility of all phosphorus-laden structures, particularly the nuclei of all cells, the nervous system, and the adrenals, to the oxidase of the blood. There results, therefore, general retardation of metabolism, particularly its catabolic phase; this is well exemplified by the hypothermal phenomena, the general functional torpor, the accumulation of fat, and the extravasation of fluids which constitute the cutaneous œdema, the latter being due mainly to passive relaxation of the peripheral blood-vessels. Wastes, detritus, etc., accumulate in the blood also as a result of defective catabolism, giving rise to "rheumatic" and cutaneous disorders. The dystrophies of various kinds with a marked tendency to degenerative processes invariably witnessed in this disorder are also normal results of defective metabolism. Considered in this light the disease may be defined as follows:—

Myxœdema is a functional disease due to marked or complete hypothyroidia when the latter occurs after puberty. It is characterized by deficient oxidation and catabolism, the main symptoms of which are hypothermia, infiltration, and swelling of the cutaneous tissues, including those of the face, increase in weight, dryness of the skin, marked weakness, and mental torpor.

SYMPTOMATOLOGY AND PATHOGENESIS.—The deficient oxygenation is well exemplified by the correspondingly depressed heat production. These patients suffer almost continuously from cold; their temperature, both oral and rectal, being always sub-normal—as low as 93° F. in some instances—unless some fever be present. In a case observed by Hun and Prudden, the temperature fell steadily until it reached 66° F., before death. The least exposure to cold causes the lips, nose, ears, and fingertips to become cyanotic; hence the abundance of covering with which these cases are found provided. The extremities are, as a rule, cold and often purple or livid. This is partly due, however, to the cardio-vascular weakness referred to below.

The deficient metabolism and functional activity is well exemplified by its influence on the cardio-vascular system, the

functional torpor of which (partly due to similar condition of the vaso-motor system) gives rise to the pre-eminent symptom of the disease: the peculiar œdema of the skin and mucous membranes. This phenomenon, which led Ord to designate it "myxœdema," is a "jelly-like swelling," as he termed it, which causes the body, particularly the face and suprascapular regions—commonly the seat of cushions or pads—to become irregularly swollen. The infiltrated tissues are elastic, firm, and resistant, but do not pit on pressure, as in true œdema, though they vibrate under lateral stroking. At first the swelling may disappear temporarily or change situation, but after a time it becomes permanent. The abdominal walls being likewise affected, the abdomen appears enlarged and pendulous, with more or less projection of the umbilicus, and sometimes ascites. The genitalia are similarly tumefied as a rule. The hands are also thickened and sometimes spade-like; the nails are brittle and thin, sometimes abnormally curved and ridged, and occasionally undergo atrophy. A similar condition may affect the toes. The forearms, legs, and feet are also the seat of swellings.

The skin, its glandular elements and the hair, all show clearly the effects of defective trophic conditions. The skin, mainly owing to the arrest of its sebaceous and sweat glands, is dry, rough, and scaly, though that of the face may be relatively smooth. It may desquamate in flakes or in the form of a fine powder. Patches of pigmentation varying from yellowish brown to the actual bronzing of Addison's disease (thus affording additional proof of the participation of the adrenals in the functional torpor) are occasionally witnessed.

The hair also changes in appearance; it becomes coarse, lusterless, and breaks easily. It is gradually lost, falling out in patches, at first where the traction attending the use of the comb is greatest, *i.e.*, where the hair is parted, the brow, and the occiput. The lashes and eyebrows are also lost in part, along with the hair of the rest of the body.

As a result of the cutaneous thickening and infiltration, the face becomes coarse, expressionless, and mask-like. The lips, greatly thickened, are usually cyanosed and cause the mouth to appear greatly enlarged. The color of the skin is yellowish or wax-like, a circumscribed patch of redness being present, as a

rule, below each cheek-bone. The nose is cold, the tip being sometimes cyanosed; it appears broad and flat through thickening of the nostrils. The ears, being in a similar condition, are likewise enlarged; the auditory meatus, however, is narrowed by its thickened walls, causing more or less deafness. The lids droop over the eyeballs—though exophthalmus may occur, due to primary exophthalmic goiter—causing the patient to appear sleepy, while an effort to raise the upper lid is manifested by elevation of the eyeballs. There is usually considerable lachrymation, due to glandular leakage.

The mucous membranes being involved, as is the skin, those of the mouth and naso-pharyngeal cavities appear pale and tumefied. That of the cheeks is indented by the teeth, against which it presses, and is sometimes bitten; this applies also to the tongue. The teeth tend to decay, and may become black within a comparatively short period, owing mainly to deficient calcium metabolism, or readily break off and fall out. This is greatly aggravated by the recession of the gums and the readiness with which these structures tend to ulcerate and bleed. Stubborn stomatitis, with free salivation, dribbling from the corners of the mouth, and erosions of the buccal, pharyngeal, and laryngo-tracheal membrane, may appear. (Edema of the larynx is not infrequently a cause of death. In some cases, however, the whole oral cavity is uncomfortably dry. The entire alimentary canal, down to the rectum, is also more or less infiltrated, causing anorexia, gastro-intestinal disorders, and constipation, which may alternate with attacks of diarrhœa. There is, as a rule, a profound distaste for meat, which in fact is toxic in a measure to these cases—as it is in thyroidectomized animals—owing to their impaired antitoxic functions.

The tumefaction of the oral mucous membrane and of the palate, tongue, and lips renders enunciation very imperfect and jerky; this condition being aggravated by the narrowing of the naso-pharyngeal lumen, it gives what voice there is a “nasal” character. It is also rendered coarse and low, that of a woman being sometimes lowered sufficiently in pitch to recall that of a man. Approximation of the cords being rendered difficult by the tumefaction, speaking sometimes requires considerable effort. The slow intellection from which these cases suffer—owing to

difficult metabolism of the organ of mind—increases greatly the trouble they experience in understanding questions and expressing their wants and ideas, a fact which often renders them extremely irritable. Mental disorders are frequent in these cases. Total lack of interest in their surroundings, somnolence, and amnesia are commonly observed.

The deficient oxidation of all muscular elements entails a corresponding weakness. Great lassitude with exhaustion upon the slightest exertion is the rule. Some cases are unable to raise the head at all or to stand. Others lapse into paralysis. Fibrillary tremor and muscular quivering are often noticed. Locomotion is tentative, often waddling; missteps are frequent, being produced by a slight obstacle. The ataxic gait may prevail; the motions of the arm are also uncertain and unsteady in sufficiently advanced cases. Although the parathyroids have been found sclerosed along with the thyroid in these cases, tetany is very rarely observed—a fact which further suggests the functional unity of these organs.

Sensation being, as a rule, markedly impaired, while the finger-joints are stiffened, the usefulness of the hands is greatly compromised. Small objects are held with considerable difficulty, and easily dropped, while such diminutive articles as pins, needles, and even small buttons are not felt at all. Tingling, formication, and pruritus are often complained of. Although cutaneous sensibility is greatly impaired, pain in the muscles and joints, neuralgia, and marked headache localized in most instances in the occipital region occur in about one-half of the cases. These are due to the accumulation of toxic intermediate waste products in the blood, owing to the deficient antitoxic power of the latter.

The senses of smell and taste are commonly impaired or perverted, the patient complaining of foul odors, a bitter or acid taste, etc. Vertigo is a relatively frequent symptom. The vision is occasionally dimmed and optic atrophy has been observed. Tinnitus aurium is not uncommon, and the hearing is impaired in the majority of cases.

Hæmorrhages from one or more organs are common. Epistaxis, hæmoptysis; bleeding at the gums, which may prove severe on extracting a tooth; intestinal, uterine, and even cere-

bral hæmorrhages may occur. Probably the most common, however, is menorrhagia. Postpartum hæmorrhages are also common in these cases. The menstruation is irregular, as a rule, and often ceases altogether until appropriate treatment procures recovery. This condition is mainly due to the poverty of the blood in fibrin ferment, as shown by the prolonged coagulation time, and to the relaxation and pseudo-fatty changes ("pseudo" because they are temporary) throughout the cardiovascular system. It is aggravated by the weak heart action, especially in advanced cases, in which the heart is deprived of the aid the adrenal secretion affords its muscular elements. The pulse is slow and weak and sometimes quite difficult to locate. The *vis-a-tergo* motion of the blood in the peripheral capillaries is slowed to a marked degree as soon as the disease has reached beyond the initial stage. To this is mainly due, in fact, the dense œdema which is the most evident characteristic of the disease.

The specific gravity of the urine varies but little; on the whole, however, it is somewhat reduced; but the urea excretion is diminished in most cases, and markedly so when the disease is advanced. In the latter case, both albuminuria and glycosuria (probably alimentary) may occur, but disappear when the thyroid treatment is instituted. Casts are also found in advanced cases.

Myxœdema progresses slowly, a case lasting, as a rule, from six to twenty years, unless the patient is carried off through some intercurrent trouble, which is often the case. Tuberculosis and pneumonia are the infections to which they seem to be especially vulnerable—owing to the enfeebled condition of their auto-defensive resources. Nephritis, pericarditis, and cerebral hæmorrhage seem to be next in the order of frequency. Periods of amelioration sometimes occur, but sooner or later the patient relapses into his previous state, and gradually dies of exhaustion. Rarely, especially in young adults, the disease may run its course in less than six months.

Acute myxœdema with prompt death may occur as the result of sudden arrest of the functions of the thyroid. In a case reported by Lloyd, the disease proved fatal in a few days. In another instance it occurred as the result of an injury to the

thyroid. It may appear as a sudden complication of goiter; it is probable, however, that under these conditions we are dealing with some toxæmia of thyroid origin rather than with true myxœdema, since we know that even extirpation of the thyroid does not produce death rapidly.

The thyroid gland is distinctly reduced in size in about 75 per cent. of the cases of myxœdema, its outline being hardly discernible by palpation in some of these. Conversely, some are abnormally large at first, and many then gradually atrophy irregularly, the portion which fails to decrease in size being resistant to pressure.

ETIOLOGY AND PATHOGENESIS.—Women are much more liable to the disease than men, *i.e.*, it occurs about six times in women to once in men, and it may develop at any time of life, though the period between the thirtieth and sixtieth years shows by far the largest proportion of cases. There is a marked familial influence, some families showing several cases. While hypothyroidia, alcoholism, and syphilis are likely to be the predominant parental factors in progressive hypothyroidia or true myxœdema, tuberculosis and neuroses are met with much more frequently in the family antecedents of the patient. The main causes appear to be rapid child-bearing, the menopause, worry, mental shocks, and injuries, especially to the head. Neoplasms, fungi, and entozoa capable of destroying or inhibiting a sufficient area of the gland have also been known to cause the disease.

PATHOLOGY.—The characteristic lesion in the thyroid is atrophy, due to the development of fibrous tissue, the glandular elements of the organ being reduced in proportion. It may follow local inflammatory lesions in connection with acute articular rheumatism, erysipelas, syphilis, actinomycosis, cancer, an acute thyroiditis, local injuries, etc., which serve to destroy a part of the glandular parenchyma, and annul in proportion its secretory functions. Excessive child-bearing, shock, and the menopause can hardly be regarded as causes of an inflammatory process, however, and it is probable that we are dealing, in this connection, rather with functional exhaustion of the organ, or with an endarteritis or periarteritis of its vascular supply.

TREATMENT.—The use of thyroid gland in this disease, introduced by Murray, is rightly considered one of the great steps in modern medicine. As in the case of hypothyroidia, however, large doses should not be used; this rule is all the more applicable to myxœdema in view of the marked relative weakness of the subjects. Again, exertion of any kind should be avoided while taking thyroid; two of Dr. Murray's cases died of syncope during active exercise taken too early after a prolonged treatment, though it must be said that he used larger doses than are now recommended. One grain (0.066 Gm.) of the desiccated thyroid, three times daily, suffices to begin with; this dose may be gradually increased $\frac{1}{2}$ grain (0.033 Gm.) until 2 grains (0.132 Gm.) are given at each meal, and until the temperature is raised to normal. If this is exceeded the dose should be reduced to $1\frac{1}{2}$ grains (0.099 Gm.) or less. The pulse should also be watched, an increase of fifteen beats indicating the need of reducing the dose. I prefer these divided doses to the single daily, but correspondingly larger, dose recommended by some observers, as the latter has seemed to me to increase the likelihood of untoward effects. Cases vary considerably in this respect, however, and the tolerance of each case should be carefully studied. The patient should spend his time in an arm-chair during the day, at first, if possible, in the open air, and begin to walk around only when his temperature and pulse become normal.

The effect of the remedy is to cause gradual disappearance of all the morbid symptoms, but if its use is discontinued they as surely return. Two grains (0.132 Gm.) daily suffice, however, to perpetuate the recovery in most instances. Before the introduction of the thyroid treatment, the disease was fatal in practically every instance. Grafting of thyroid is now used successfully to prevent the need of constantly taking thyroid gland. The measure is described on page 200.

When the asthenia is marked and the heart, as is usually the case under these conditions, is considerably dilated, a small dose of digitalin, $\frac{1}{20}$ grain (0.0033 Gm.), three times daily, or the desiccated suprarenal gland of the U. S. P., or, better, the pituitary gland, 1 grain (0.066 Gm.) during meals, greatly hastens the curative process.

INFANTILE MYXŒDEMA, OR CRETINISM.

Although cretinism is, like myxœdema, due to loss or impairment of the functions of the thyroid apparatus, its symptomatology differs in many respects from that of myxœdema, because, as previously stated, it occurs during the period of life when growth and development, physical and mental, are most active, i.e., between birth and puberty, whereas myxœdema includes only cases that occur after puberty. In cretinism we witness the results of defective oxidation and metabolism of cellular proteids and fats at a time when the building up or anabolic phase is exceptionally active, and, as a result, arrest of physical and mental growth. The following definition seems to me to include the main features of the disease:—

Infantile myxœdema, or cretinism, is a functional disease due to marked or complete hypothyroidia during the period between birth and puberty. It is due to deficient oxidation and is characterized by retardation of physical and mental development, the main symptoms of which are: stunted growth, the cretinic facies with flattened nose, thickened lips and tongue, a harsh skin, and more or less advanced idiocy.

SYMPTOMATOLOGY AND PATHOGENESIS.—The disease may develop *in utero*, but it is seldom recognized before the first month. The attention is drawn to the child through the fact that it fails to grow at the average rate either physically or mentally. Its tongue is then noticed to be unusually thick—sufficiently so, in some instances, to project beyond the lips at all times, fill the oral cavity, and interfere with the respiration when the child lies in the recumbent position.

Closer examination then reveals the symptoms witnessed in adult myxœdema. The “jelly-like swelling” of Ord, coupled with the yellowish, white, or waxy pallor, the rough, dry, and scaly skin, so unlike that of a normal child, is clearly defined, though the puffy face retains some of its smoothness. The fontanelles remain patent unusually long. The features of the cretin are, as a rule, repulsive, though pitiful. The swollen, often wrinkled brow; the puffy lids, which reduce the watery eyes to mere slits; the “saddle-back,” or depressed, nose with its wide and thick alæ; the swollen, erect ears; the large and drooling

nor laughs. It is absolutely apathetic, sits quietly without manifesting any special wants. It may, however, show signs of hunger or thirst, either by crying like an infant or by grunts or inarticulate sounds. In a higher grade, a few words may be spoken, there is recognition of parents and familiar faces and even a show of affection for them, but beyond the limited vocabulary no progress can be made, even the alphabet being beyond them. Still higher grades may speak fairly well, be free, though slow and deliberate, in their movements, etc., but fail to develop thereafter, even if they attain old age, which is not often the case.

The brothers Wenzel have divided these cases into three classes: the *cretins*, who are unable to speak, and lead a purely vegetative life; the *semi-cretins*, who are simple-minded, but whose language is limited and imperfect; and the *cretinoids*, who are endowed with some intelligence, but show the physical signs of cretinism. There is another type, the *mongolian*, called thus because of their slanting eyes, which closely resembles the cretin of a higher order, but this type shows more intelligence and seldom yields to the effects of thyroid preparations.

The thyroid, in about two-thirds of the cases, is more or less atrophied, to such a degree in some that it cannot be detected by palpation. In the remaining third, and usually in the endemic cases, there exists a more or less developed (sometimes voluminous) goiter.

ETIOLOGY.—It becomes necessary in this connection to distinguish between the two general classes, endemic and sporadic cretinism.

Endemic cretinism, often a family disease, and observed in a number of cases in special localities, is believed to be due to some chemical substance or micro-organism peculiar to the waters available in those regions.

This type has been connected with special localities by proofs from various directions. Not only is cretinism common in these regions, but normal individuals may, on moving to them, have cretinic children therein, and normal children in healthy regions. Again, animals from the latter were found to develop goiters (the preliminary cause of endemic cretinism) in the contaminating districts by drinking their water, while this

water carried afar to healthy localities and given to dogs as sole beverage also caused goiter in these animals. Whether it is a mineral salt, a vegetable mold or some other pathogenic micro-organism is not established, but for the time being the germ theory seems to prevail.

The question of heredity in these cases is a debated one. We have seen under "hypothyroidia" that syphilis and alcoholism tend to leave their imprint upon the thyroids of descendants. Some oppose this view in respect to cretinism on the ground that the positive signs of cretinism only appear when the child is weaned, and contaminating water is given to it. But this is obviously wrong: Cretinism can readily be detected in a child one month old and earlier by observers who are thoroughly familiar with the morbid effects of hypothyroidia. The latter condition in the mother is also well known to result in hypothyroidia in her offspring—a fact which brings us back to any maternal defect inherited, such as hypothyroidia, syphilis, alcoholism, etc., that may be present as the origin of the hypothyroidia in the child. In other words, there is at present no sound foundation for antagonism to the prevailing view that endemic cretinism may be congenital in a certain proportion of cases.

Sporadic cretinism, which has also been termed "cretinoid," or "*myxedematous, idiocy*," and "*cretinoid pachydermia*" occurs in any country, in localities that are entirely free from cretinism, and in healthy families. It is mainly due to some lesion of the thyroid caused by an acute febrile disease or some intoxication capable of inhibiting or arresting its functions, either before or after birth.

How a general infection can produce such lesions in the thyroid is admittedly unknown. From my viewpoint, it finds its explanation in an autodigestive process similar to that which occurs in the pancreas under certain conditions. As previously stated, I have attributed to the thyroid secretion properties similar to those of Wright's opsonins, a view recently sustained by Marbé and Stepanoff, at the Pasteur Institute. The antitoxic and antigerm constituents of the blood circulating in the thyroid (and parathyroids, which may also be the seat of similar lesions), it is obvious that undue accumulation of thyroid secretion in the

organ itself will oversensitize its own parenchyma or its vascular elements or both, and render them vulnerable to proteolysis—along with any germ or toxin that may be present in the organ. The autodigested areas are replaced by fibrous tissue, and a process of cirrhotic atrophy is started which sooner or later annuls the functions of the organ.

The diseases which have shown themselves to be the most frequent causes of sporadic cretinism are typhoid fever, scarlatina, pneumonia, and pertussis—the identical series which proves most prolific in the genesis of the infantile encephalopathies, another source of idiocy, but in which the cerebral lesions are the direct pathogenic factors.

PATHOLOGY.—The end lesions are the same in both forms. In the endemic form there is a marked proliferation and overgrowth of interstitial tissue or connective tissue, causing both enlargement of the gland—goiter—and obliteration of the glandular tissue. Some glandular tissue usually persists; even this remnant, however, shows evidences of degenerative change.

The symptomatology of both forms indicates clearly, we have seen, that deficient oxidation, metabolism, and nutrition underlie the resulting general physical phenomena. This applies as well to the mental phenomena, symmetrical arrest of development affecting more or less all the elements of the brain. There are occasionally found localized lesions of the nature of infantile cerebropathies, porencephaly, etc., but it is probable that these are concomitant changes rather than components of the typical picture of cretinism *per se*. Briefly, we are dealing with arrested nutrition and development of the brain as a result of the absence of the secretion which sustains these fundamental processes.

TREATMENT.—Before the introduction of thyroid gland in the treatment of this distressing condition, there was practically nothing to be done. While its use must be continued, relapse (excepting the body growth) occurring invariably without it, though, as a rule, with much less intensity, the fact remains that the changes produced in the child, particularly in sporadic cases, are truly marvelous. As early development of the disease inhibits the mental development accordingly, the later in childhood it appears, the better are the results of treatment, in so far

as the intelligence is concerned. The physical restoration is not materially influenced by the age at which the disease first appeared. Children grow with surprising rapidity in some instances, over one inch per month in some cases, until the normal stature of the corresponding age is reached. The brain responds more slowly; but considerable intelligence is gained, though it does not reach, as a rule, that of normal children. They learn slowly and develop only very gradually their vocabulary. They should be gently assisted in this direction.

When the thyroid treatment is instituted the case should be carefully watched, as the tolerance varies greatly in different children. They should be kept from any violent exercise lest heart-failure occur. Another important reason for this precaution is the fact that the growth of the skeleton is so rapid that the bones tend to soften, and, therefore, to yield and bend. The tibia and fibula are especially exposed; braces should be applied to offset this tendency if it shows itself, until the normal height of a child of a corresponding age has been attained. Syrup of calcium lactophosphate of the U. S. P., one teaspoonful or less, according to the age, is a useful adjuvant to thyroid gland in this connection. This is accounted for in the opinion of Parhon and Papinian¹¹ and others, based on many published facts, that the thyroid gland plays an important rôle in the assimilation of calcium.

Large doses are not only dangerous, but they inhibit the beneficial process. Again, it must be remembered that the thyroid active principle is cumulative in the sense that the organism will utilize a certain quantity—which varies with each case—and that any excess may prove toxic. This stage may be reached early in one instance and late in another. I have seen it produced in three weeks with 2-grain (0.132 Gm.) doses; conversely, in a case reported by Freund in a girl of 14 years, 6 grains (0.396 Gm.) daily in divided doses caused a sudden rise of temperature to 104° F., a pulse of 160, rapid breathing, and death the next day, though she had been taking the same agent nineteen months. The *danger signals* are rapid pulse, vertigo, general weakness, pains in the back and limbs, syncope, and, if

¹¹ Parhon and Papinian: *România medicală*, 1904, cited in "Sécrétions Internes," p. 17, 1909.

the intoxication be severe, nausea and vomiting, a marked rise of temperature, and collapse. When any untoward effect occurs, cessation of the remedy a few days suffices. They are more likely to appear when the preparation used is old, a fact which suggests that it may have undergone putrefactive changes when long kept.

An infant can be given $\frac{1}{2}$ grain (0.033 Gm.) daily of desiccated thyroid, and a child of 2 years, twice daily, and older children thrice daily, or 1 grain (0.066 Gm.) can be given at dinner and another on retiring. I have never seen such doses produce untoward effects, the recumbent position after the second dose, as urged by Murray, preventing them. When it is necessary to increase the dose, the patient should be seen frequently. As much as 5 grains (0.33 Gm.) have been given three times daily with safety; but it must be remembered that the preparations now available are better and more efficacious. The preparation I now use is Burroughs, Wellcome & Co.'s standardized desiccated gland substance (in tabloids), which contains 0.2 per cent. of iodine in organic combination. Cretins usually stand larger doses than others. A good guide in them is the temperature, which tends to rise to normal; as a rule, the dose that will do this suffices to bring about the desired results. When this is attained, 1 grain (0.066 Gm.) on retiring suffices to prevent recurrence. But it must not be neglected; otherwise, the disease will certainly return.

The younger the patient, the more marked the improvement, as a rule. In adult cretins, the results are meager if any at all are obtained. The improvement is much more marked in sporadic than in endemic cases, owing probably to the fact that up to the onset of the causative disease physical and mental growth had proceeded normally. In the Mongolian type, the thyroid treatment is useless.

Grafting of thyroid tissue to render the constant use of thyroid preparations unnecessary has been tried by various investigators. It is only in recent years, however, that a promising method has been introduced by Christiani,¹² of Geneva. The conditions are that only normal and living tissues be used; that the grafts be small (about the size of a grain of wheat), but

¹² Christiani: *Semaine médicale*, March 16, 1904.



Fig. 1

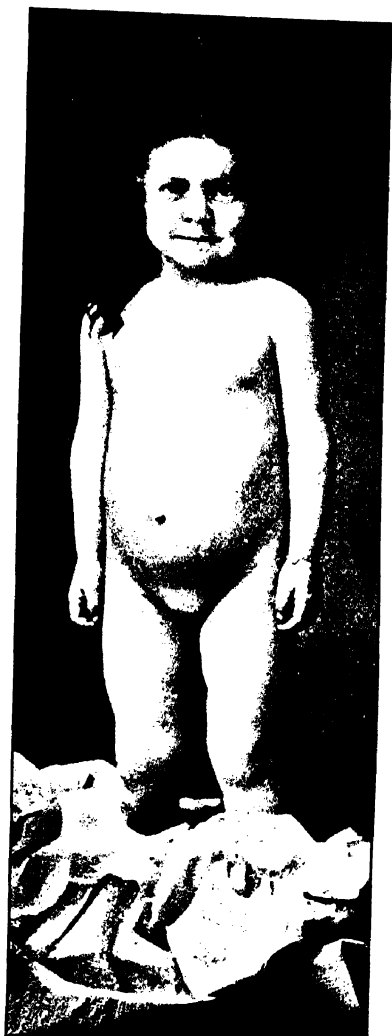


Fig. 2

THYROID EXTRACT IN CRETINISM. [C. C. Mearns.]

Fig. 1. Cretinoid idiot 7 years old when thyroid treatment was begun. Had ceased to develop when 3 years old.

Fig. 2. Changes after one year's treatment. Height, 31½ inches.

[Cleveland Medical Gazette.]

very numerous; that they be inserted in very vascular subcutaneous cellular tissue, and that only human thyroid be employed. This makes it possible to obtain small grafts from a removed goiter containing areas of normal tissue, and to transplant them into the cretinous subject. The tissue can be kept alive an hour in physiological saline solution. A very sharp instrument should be used to cut the grafts to avoid crushing them. They are then introduced *in situ*, where they gain a perfect foothold, becoming perfect thyroid parenchyma. More recently, Charrin and Christiani¹³ obtained good results with sheep's thyroid. Six months after the operation, the patient (a case of operative myxœdema) became pregnant, and it was found that each graft became enlarged, in keeping with the physiological process which occurs normally in the gland proper under similar circumstances. Christiani¹⁴ reported distinct improvement in 60 per cent. of his cases, which included myxœdema, cretinism, dwarfism, etc., remarkable results in 34 per cent., and no result in 6 per cent. The most striking results were in the various types of cretinism.

MYXŒDEMATOUS INFANTILISM.

This disorder, first attributed to the thyroid by Brissaud, resembles cretinism very closely, but its retention as a separate class is warranted by the fact that the arrest of development manifests itself mainly by the persistence of the characteristics of childhood, physical and mental, without the evidences of true idiocy, and often without dwarfism. The thyroid apparatus, either through inadequate development of congenital origin, organic lesions, especially sclerosis, acquired in the course of acute infections during infancy, or from some other cause, is unable to supply enough of its secretion to subserve the needs of both metabolism and growth (which involves an excess of metabolic activity), and the latter ceases, while normal metabolism, enough to sustain the vital process, continues.

SYMPTOMATOLOGY AND PATHOGENESIS.—The worst cases, in which myxœdema predominates, are virtually instances of

¹³ Charrin and Christiani: *Le bulletin médical*, July 11, 1906.

¹⁴ Christiani: *Bull. de l'Acad. de méd.*, vol. lviil, 1907.

cretinism of a mild type. The patient is short, thick set, and obese, though child-like in shape, and may look old for his age. The face appears bloated, rounded, pale, and wax-like, a reddish patch being sometimes present below the cheek bones. The nose squatty and pugged, and the mouth large; the latter is usually open,—a fact accounted for by the almost invariable presence of adenoids, hypertrophy, and infiltration of the nasal mucosa and tonsils. The tongue, as in the cretin, may be thickened and the lingual tonsil likewise, rendering speech thick and difficult. The hair may be profuse, though coarse and lusterless, but about the eighteenth year it begins to fall in patches, leading, in most instances, to alopecia. In most cases hair fails to grow on other parts of the body. The skin is tense, owing to infiltration, and is also dry, because of deficient action of the cutaneous glands, and it feels rough and scaly to the touch. Pruritus is often complained of.

The teeth remain infantile, as a rule, and decay early. The abdomen is unusually prominent and hard in all cases, owing, mainly, to the stubborn constipation which causes retention of gas and feces, the latter being only voided in some cases by engorgement and to relaxation of the abdominal muscle. The constipation is also mainly due to the loss of tone of the intestinal muscular fibers and the paucity of succus entericus. Enuresis is commonly observed. Although the respiration is apparently normal there is deficient oxidation; the extremities are cold and are readily affected with chilblains in cold weather. The face and extremities may even be cyanotic and the patient complain of constantly feeling cold. Actual hypothermia is a common feature of these cases. The part played by the thyroid in this phenomenon is well shown by the fact that Beebe¹⁵ found that "by the administration of thyroid to a cretin or patient with myxœdema it is possible to increase the absorption of oxygen from 20 to 75 per cent."

The difference between this form and true cretinism lies, as stated, in the fact that idiocy does not occur. The child may not be bright or even normally intelligent, having been slow to talk and shown deficiency at school, particularly in spelling, grammar, and arithmetic, but it is, nevertheless, quite able to

¹⁵ Beebe: *Loc. cit.*, p. 659.

hold its own for all ordinary needs; the face, in fact, unlike that of the cretin, bears an expression of intelligence. Yet the intellect retains the characteristics of childhood, both as to ideas, judgment, and emotions, a patient of twenty years, for example, preferring the company of children below ten to that of young men of his own age. These patients may show a proclivity to lie, steal, start fires, etc., especially when under the evil influence of designing normal individuals. Any unlawful act they may commit is due, in most cases, more to lack of judgment and inability to resist suggestion and a desire to please others than to an inherent proclivity to crime. Others are excitable, turbulent, and rough, and frequently break anything that is at all fragile; here, again, the element of willful harm is absent, muscular tremor and inability to prevent movements of the hands or fingers—as in athetosis—being the underlying cause of the defect.

The heart is excitable, a slight emotion sufficing to cause violent “palpitations” and tachycardia. This is mainly due to a deficiency of adrenal secretion. Dilatation of the heart from the same cause is often witnessed. The veins also show a marked tendency to dilate, the veins of the extremities and the hæmorrhoidal veins particularly. Varicocele may also exist. In a case seen through the kindness of Dr. W. Egbert Robertson, a sprig of thick veins spread upward over the mons veneris and coincided with undeveloped testicles and total absence of hair over the genitalia, in a young man of twenty years. Hæmophilia is frequently noted, an indirect result also of the hypothyroidia, since thyroid gland given orally counteracts hæmophilia by increasing the coagulation time. Epistaxis, menorrhagia, and metrorrhagia are also observed in some cases, the two latter phenomena where menstruation has developed at all, which is often not the case, coinciding with non-development of the breasts and pubic hair. The penis and testicles often remain rudimentary even when the male reaches full adult age, and his general shape and high-pitched voice recalling those of a woman.

In a still higher type of infantilism the signs of myxœdema are hardly discernible. The growth may even exceed that of the average individual. Such cases are usually plump and even

portly; as in the preceding form, the abdomen tends to be large, but the limbs are well rounded, recalling those of a woman, with fair skin, a high-pitched, or infantile, voice to complete the resemblance. The face, axillæ, and pubis are free of hair; the penis and testicles small and rudimentary. Mentally "he is simply an overgrown child," wrote Meige,¹⁶ who gave us a close analysis of these cases. "These children, who should long before have reached the reasoning period of their lives, play with toys, laugh at a childish prank, cry for practically nothing, become angry as readily, are subject to ridiculous frights, and call their mamma under the influence of the least emotion." In the average case, however, this truly infantile type—recalling the behavior of a child of but two or three years—is better exemplified by one of seven or eight years, though he be perhaps actually beyond his twentieth year.

The feminine attributes are sometimes very marked in the male, the breasts, thighs, and general conformation resembling closely those of the female, constituting the "feminine" type. In the female, in whom infantilism occurs less frequently, the body preserves the attributes of childhood, *i.e.*, it fails to undergo the normal changes of puberty. Though tall, perhaps, the body shows no development on sexual lines: the breasts remain small and flat, no hair grows in the axillæ or over the pubis, the trunk remains cylindrical, and the hips and nates flat. The uterus and its adnexa also fail to develop, and menstruation fails to appear. Some cases tend even toward the male sex, constituting "masculinism," the voice, the physical outline, assuming a masculine type.

DIAGNOSIS.—From this type, which belongs essentially to the domain of the thyroparathyroid apparatus, must be distinguished several types which do not.

Lorain Type of Infantilism.—In a type described by Lorain, in 1870, the dwarfism is symmetrical in the sense that the ultimate products are symmetrical, miniature men—this form being practically always observed in the male. No myxœdematous symptoms are present; the genitalia are usually normal, though the pubic and axillary hair is wanting, and notwithstanding their diminutive stature and their slender physique,

¹⁶ Meige: *Revue Intern. de Méd. et de Chir.*, Mar. 25, 1896.

their facial appearance and expression, and their intelligence are usually quite up to the average. They depart in no way from their fully developed fellow-men, in fact, except in the stature. As shown mainly by Meige,¹⁷ this type is not due to thyroid insufficiency, but to anangioplasia, *i.e.*, defective development of the arteries and premature ossification. It is usually ascribed to parental hereditary syphilis, tuberculosis, alcoholism, and other debilitating disorders. Thyroid preparations in this form are of no value.

Mongolian Infantilism.—This type is characterized by Mongolian features, and particularly the slanting eyes. These features occur at birth, and are not traceable to syphilis, tuberculosis, alcoholism, etc., as in the Lorain type, but rather to prolonged deliveries—which account in some cases, at least, for the flat skull or bulging forehead—or to strong mental emotions during pregnancy. They are not morose or torpid like the myxœdematous cases and are usually amiable and well behaved. Curiously enough, all show a marked predilection for music and signs of unusual development of the musical sense. The tongue is usually quite thick and heavy, and the hands square and flat, the latter accounting for the clumsiness which characterizes all these cases. They usually suffer from some chronic respiratory trouble, and are apt to die early of some intercurrent infection. Their undeveloped size, their Mongolian facies, the bulging forehead, and their feeble-mindedness render the recognition of these cases quite easy. Thyroid preparations are of no avail.

Achondroplasia, or Fatal Rickets.—This type of dwarf, unlike the myxœdematous type, does not show mental deficiency, but many of the characteristics of cretinism: the relatively large head, the saddle nose, the short and bowed limbs, the prominent abdomen, and the marked lordosis. But the arms and legs are, unlike the other types, which all show some degree of symmetry, entirely too short for the body, the finger-tips never reaching the level of the hips. Again, the long bones are usually bent and deformed. The skull is unduly developed and is out of proportion with the face, which is then made to appear small. The eyes, lids, and tongue may resemble greatly those of the cretin, but the hair is normal and usually abundant, and the

¹⁷ Meige and Allard: *Nouvelle Iconog. de la Salpêtrière*, No. 2, 1898.

skin soft and well nourished. These characteristics, the fact that the mental faculties are quite normal, and the ineffectiveness of thyroid treatment render the identification of achondroplasia quite easy.

TREATMENT.—The only measure of any value in myxœdematous infantilism is the use of thyroid preparations. The treatment recommended for cretinism being as applicable here, the reader is referred to page 198. The younger the patient, the greater are the chances of improvement. After puberty has been reached, the results, in so far as the mental status is concerned, are seldom satisfactory.

THYROID HYPERÆMIA AND THYROIDITIS.

This is a very important disorder mainly because of its causative influence upon the conditions just reviewed, *e.g.*, hypoparathyroidia, myxœdema, and cretinism, and the whole gamut of morbid effects of deficient functional activity of the thyroparathyroid apparatus. It is generally recognized in its acute form when the inflammatory phenomena are very marked, but, unfortunately, it is not only in this class of cases that lesions in the organ are provoked. The structure of the thyroid is such, and the quantity of blood circulating through it is so great, that a high blood-pressure, such as that which occurs during high febrile processes, is sufficient to produce areas of interstitial hæmorrhage in the interlobar connective-tissue spaces, which form as many sclerotic areas wherever the damage done has been sufficiently great. As nature provides an excess of thyroid tissue over and above the needs of the organism, however, inhibition of a proportion of the gland below this limit may prove harmless, but if the sclerosis happens to exceed this limit the result is a more or less marked hypothyroidia (or hypoparathyroidia if the parathyroids are involved, which is at least sometimes the case) corresponding in severity with the proportion of thyroid tissue sacrificed. Indeed, we have seen that in all the disorders treated so far in the present chapter sclerosis of the thyroid, with its resulting atrophy, was by far the most prominent pathogenic lesion.

The graver condition, acute thyroiditis, is fortunately comparatively rare. Moreover, while simple hyperæmia, even when

attended by interstitial hæmorrhage, is seldom recognized, acute thyroiditis is attended by severe local and general phenomena, which make it possible to identify it early, to meet it therapeutically and avoid disastrous results. Acute inflammation of the thyroid—apart from that due to the presence therein of goiter, cancer, etc.—is usually provoked by invading bacteria in the course of infections, notably: diphtheria, typhoid fever, scarlatina, measles, parotitis, tonsillitis, erysipelas, pneumonia, pertussis, dysentery, rheumatic fever, puerperal fever sepsis, orchitis, and influenza. It has also been attributed to the action of poisons, constituting what has been termed “toxic thyroiditis”; iodine and the iodides have also been known to cause it along with other signs of iodism. In these inflammatory disorders the glandular tissues undergo marked changes, including desquamation and degeneration of the epithelium, besides the interstitial sclerosis met with in the form previously described. If the area thus affected is large, the functions of the gland may become sufficiently impaired to constitute marked hypothyroidia, which, we have seen, may, in children, arrest general development of both the body and mind. Shields¹⁸ witnessed an instance in which thyroiditis lasting one week led to complete atrophy of the organ and to typical cretinism. In a case reported by Bonney^{18a} the left lobe was converted into an abscess cavity.

SYMPTOMATOLOGY.—Though capable of doing considerable injury to the gland, the acute hyperæmia attending infectious diseases gives rise to few tangible phenomena, *i.e.*, slight swelling of the neck, sensitiveness to pressure, and, perhaps, slight pain during deglutition. Unless looked for, they will seldom be discerned, as they do not cause sufficient discomfort to attract the attention of the patient.

In acute thyroiditis the onsets, usually ushered in by a chill, is generally sudden; the most marked symptom is difficulty in swallowing with, sometimes, neuralgic pain which radiates widely in various directions, the ears and neck, even to the arms and occiput; this is sometimes very severe, particularly during deglutition and on moving the head from side to side. If the whole gland is involved and the swelling, which is often the size of a hen's egg, is marked, severe dyspnœa and even cyanosis

¹⁸ Shields: N. Y. Med. Jour., Oct., 1898.

^{18a} Bonney: London Lancet, July 15, 1911.

may occur, owing to pressure of the inflamed organ upon the trachea. Paralysis of the recurrent laryngeal may occur and produce hoarseness and paroxysms of suffocation, but the hoarseness and cough are more likely to be due to involvement of the larynx in the inflammatory process. Edema of the glottis may also occur, as in cases reported by Lewis and O'Neill.¹⁹

The identity of the inflamed organ is readily established by causing the patient to swallow, when the tumor will rise, provided the head is not bent backward, which will immobilize the organ. Headache is often present and epistaxis occurs sometimes, owing to pressure of the enlarged thyroid upon the cervical veins and the passive cerebral congestion this produces. Carotid pulsation has also been observed by Broca. The surface of the organ is sometimes quite congested. There is more or less fever during the acute stage; it is sometimes quite high notwithstanding the absence of suppuration—a fact which is ascribable to the excessive production of thyroiodase. Tachycardia independent of temperature has also been noted by Parisot.²⁰ As observed by Jeanselme, the coagulating power of the blood is greatly increased. The morbid process lasts, as a rule, but a few days, the swelling subsiding completely in most instances. Occasionally a certain amount of enlargement may persist. Forty per cent. of the cases terminate in resolution, *i.e.*, without suppuration.

When an *abscess* is formed the course of the morbid process is more protracted. A single abscess rarely occurs, the glandular mass being studded with numerous purulent foci, which, if close one to the other, tend to run together. Each abscess tends to break through the adjacent soft tissues, including the skin. The trachea and oesophagus may therefore be invaded by a purulent stream when rupture occurs. Metastatic abscesses may also appear in the cervical cellular tissue. When spontaneous rupture occurs through the skin, or when the abscess is surgically evacuated, the inflammatory process recedes rapidly. When, however, it is left to itself, the purulent infiltration of surrounding parts may give rise to serious complications, by

¹⁹ Lewis and O'Neill: Jour. Amer. Med. Assoc., Nov. 12, 1910.

²⁰ Parisot: Presse Médicale, May 7, 1910.

involving, besides the trachea and œsophagus, referred to above, the mediastinum, the pleura, and the lungs proper, causing septic pneumonia, and also the large vessels of the neck and chest and thus causing pyæmia. Thyroid abscesses bleed readily and are sometimes the source of severe capillary hamorrhages.

Chronic thyroiditis may follow the acute type, either through perpetuation of the infection in some small portion of the gland or the formation of a sinus which fails to heal. In the majority of instances, however, it occurs concomitantly with chronic processes, such as syphilis, tuberculosis, echinococcus cysts, actinomycosis, etc. The prognosis in these cases is less favorable than in the acute form, since more or less impairment of the functions of the organ follow the destructive action of the abscess upon the glandular tissues owing mainly to the fibrous induration it entails in various parts of the organ. Both the acute and chronic types are prominent causes of hypothyroidia with its long train of morbid results, ranging from cretinism through its many modalities to the milder types of myxœdema described.

DIAGNOSIS.—In the acute form, the increased volume of the gland, which sometimes becomes greatly enlarged in a few hours, the sensitiveness to pressure, and the radiating pain, all located in the region of the thyroid, coupled with the fact that, on swallowing, this organ, *i.e.*, the seat of all these acute symptoms, moves up and down, render the diagnosis quite easy in well-marked cases. When, as is often the case, the inflammation is unilateral, especially if œdema of the tissues prevails, it may resemble mastoiditis or parotitis and has, in fact, often been taken up for the latter disease. Its connection with a mobile structure on the other side of the neck, however, renders the differentiation possible. If abscesses form, fluctuation is sometimes discernible. Œsophageal abscess in the neighborhood of the thyroid furnishes much the same symptoms, but the mobility of the gland during deglutition makes it possible to identify it as the seat of abscess.

TREATMENT.—The prevention of acute thyroiditis, even in its milder forms, is an important feature in this connection, when we consider its pernicious effects upon development of the child and upon the general welfare of the individual at all ages.

As previously stated, the main cause of the lesions is the excessive proteolytic activity of the intrathyroidal plasma, owing to the identity of the organ as the source of the substance which, as I have pointed out, is the homologue at least of Wright's opsonin—*i.e.*, the thyriodase. The presence of bacteria in the thyroid brings to it, as elsewhere, all the defensive constituents of the blood, both fluid and cellular. The excess of opsonins increasing the vulnerability of the thyriodal tissues to the proteolytic activity of these antibodies, however, these tissues yield readily to the destructive action of the latter. The aim, therefore, should be to prevent this complication in the course of febrile infections.

Two measures of value are at our disposal in this connection. The first of these is the local application of cold. The thyroid should be carefully watched for any complication, and if it becomes sensitive or swollen, or the patient complains of pain in the thyriodal area, cold compresses should be applied over it. The effect of cold is to reduce local temperature and through this the activity of the proteolytic enzymes which the antibodies of the blood contain. In other words, it is not bacteria which do the damage, but the excessively active germicidal substances they invite into the gland, and by reducing this activity with the aid of cold the *excess* of digestive power is antagonized. That the bacteria are less violently attacked under these conditions is obvious, but it is far better to allow the bloodstream to transfer the germs elsewhere in the body for destruction, *i.e.*, to the general circulation, where their destruction can proceed without compromising the integrity of any tissue so vital to the welfare of the body as the thyroid.

The second measure is the free use of physiological saline solution, either by the mouth, rectum, or subcutaneously, to reduce the viscosity of the blood. Not only does this counteract excessive proteolytic activity of the antibodies which underlies their destructive action on the thyroid and other tissues and cells—the underlying causes of hæmolysis and autolysis—but it facilitates osmosis and therefore the circulation through the thyroid, which has been fittingly compared by Bérard to a sponge, so replete is it with blood. Another advantage of the use of saline solution is that, as shown elsewhere (see page 1367),

it enhances the activity of the autoprotective process while facilitating the renal elimination of toxins or the end-products.

The treatment of acute thyroiditis likewise includes the use of the above measures besides the remedies the causative disease warrants. One feature of importance in this connection is that a high blood-pressure is a pernicious feature of the disorders; vascular depressants, such as chloral hydrate and veratrum viride, preferably the former, therefore, are of considerable value. J. C. Wilson has shown that chloral hydrate can be used advantageously to reduce the peripheral congestion and general distress in scarlatina. As this and other exanthemata are relatively frequent causes of acute thyroiditis, it may safely be employed to counteract this condition.

Surgical measures often become necessary. According to Kocher²¹: "The presence of pus is difficult to demonstrate and premature incision must be avoided. If necessary, the gland itself should be exposed. If incision of the abscess is not followed by rapid recovery, the presence of multiple abscesses should be suspected. Fistula points to extensive necrosis. In such a case the affected half of the gland must be excised. Partial thyroidectomy may also be considered in cases of thyroiditis that have become chronic and in chemicotoxic thyroiditis." In the chronic thyroiditis attended by hypothyroidia, thyroid gland should be given, and the actually diseased part removed surgically, especially if dyspnœa is present.

²¹ Kocher: Keen's "Surgery," vol. III, p. 380, 1908.

CHAPTER V.

DISEASES OF THE THYROPARATHYROID APPARATUS (*Continued*).

DISORDERS DUE TO EXCESSIVE ACTIVITY OF THE THYROPARATHYROID APPARATUS.

OVERACTIVITY of the thyroparathyroid apparatus, in keeping with the opposite state, described in the preceding chapter, has been identified by numerous terms, the most used of which are pseudo-Graves's disease, aberrant or larval exophthalmic goiter, incomplete Basedow's disease, *forme fruste de la maladie de Basedow*, hyperthyroidism, and thyroidism. The first five of these were based upon the fact that all of the phenomena were reproduced in exophthalmic goiter, of which the disorder is, in truth, a mild type. The absence of the major symptoms: exophthalmus and goiter, however, so readily misleads the clinician into erroneous diagnoses that the tendency of modern observers is to distinguish this milder type from true exophthalmic goiter, *i.e.*, to regard it as an autonomous syndrome, in which the cardinal symptoms mentioned above are not suggested. Hence the terms "hyperthyroidism" and "thyroidism." As stated in the preceding chapters, however, the terminal "ism" appears to me to suggest the presence of a habit rather than a morbid process subject to treatment. I prefer the term "hyperthyroidia," therefore, which, besides covering this feature, harmonizes with the terminals previously used. To simplify the term, it is not made to include the parathyroids, though, as in hypothyroidia, it must be understood that these glandules are deemed functionally associated with the thyroid proper in the process to be described.

HYPERTHYROIDIA.

(Pseudo-Graves's Disease; "aberrant" or "larval" Exophthalmic Goiter; *forme fruste de la Maladie de Basedow*; Incomplete Basedow's Disease; Hyperthyroidism; Thyroidism.)

By the above term is meant the aggregate of symptoms which excessive activity of the thyroparathyroid apparatus

awakens when the cardinal symptoms of exophthalmic goiter, *i.e.*, exophthalmus and goiter, are missing. There are still, particularly in Europe, a few observers who deny that exophthalmic goiter is due to excessive activity of the thyroid. But their opinion is based only on a few experimental facts which do not stand close scrutiny. Clinical medicine and surgery, on the other hand, backed up by many experimental data, plead overwhelmingly, however, in the opposite direction. "The whole structure of the surgical treatment of Graves's disease," writes A. E. Elliott,¹ "rests upon the theory of hyperthyroidism, and, if it be not true, then the hundreds of thyroidectomies which are now matters of record remain without justification. The striking influence over the disease, which follows a well-executed partial thyroidectomy, furnishes evidence in favor of the theory of hyperthyroidism, which is so direct as to be apparently irrefutable. The results of thyroid feeding supply evidence which is hardly less conclusive. The administration of thyroid gland substance, or thyroid extract, is capable, if given in sufficient amount, of inducing a toxic state which in almost every essential is similar to Graves's disease." That it can thus be caused both in man and in the lower animals, has been observed by Notthaft, Edmunds, and others. "An artificial state of hyperthyroidism is thereby produced," also writes Elliott, "which duplicates almost in full the morbid syndrome. Even the characteristic exophthalmic symptoms have been observed after thyroid feeding by Auld, Bécélère, and others, and Edmunds was able to induce proptosis, widening of the palpebral fissure, and dilatation of the pupils in six monkeys by this means, even after excision of a portion of the cervical sympathetic." That it is the iodine of the thyroiodase which produces it, is also shown by the statement of Kocher that excessive iodide treatment is responsible for the development of exophthalmic goiter in more cases than is generally recognized, the form produced being a severe one.

As to the manner in which such marked phenomena as those witnessed in hyperthyroidia and its aggravated form, exophthalmic goiter, by an excess of thyroid secretion, it must be frankly stated that the existing confusion is eliminated when

¹ Elliott: Amer. Jour. Med. Sci., Sept., 1907.

the functions of the thyroparathyroid apparatus are interpreted, in keeping with the conclusions submitted in the third chapter, (1) that the thyroiodase sustains oxidation and both phases of metabolism—anabolism and catabolism—by sensitizing or increasing the inflammability of the phosphorus of all tissues—including the adrenals and their center and nerves—to the action of adrenoxidase, and (2) that it participates through this same sensitizing action upon all wastes and other eliminable refuse materials in the blood and scavenger cells, in the auto-protective functions of the body, both in health and disease. These two functions once thoroughly apprehended, we shall find that the clinical history of these cases is not difficult to understand. It is perhaps unnecessary to state that the symptomatology of hyperthyroidia illustrates only the phenomena due to exaggeration of metabolism, and that the increased immunizing activity which it entails gives rise to no individual phenomena.

While, as conceded above, there is ground for the recognition of hyperthyroidia as a separate syndrome, the fact remains that its etiology, pathology, symptomatology, and medicinal treatment are practically the same as those that obtain in exophthalmic goiter. It is unnecessary, therefore, to treat the former under a separate head, the reader being requested to look upon hypothyroidia as less severe symptomatically than true exophthalmic goiter, and as presenting neither its two cardinal signs: exophthalmus and goiter, nor its progressive lethal trend, unless, as is often the case, it lapses into this severe form.

EXOPHTHALMIC GOITER.

(Parry's Disease; Graves's Disease; Basedow's Disease.)

Referring to this disease, in the earlier editions of this work,² I advanced the view that it was in conjunction with the adrenals that the overactive thyroid gland provoked what I regarded as the *sthenic or first stage* of the disease, my conclusion to this effect being: "Exophthalmic goiter is due to overactivity of the thyroid and adrenal glands, and to the exaggerated tissue oxidation this entails." We have seen that the labors of Kraus and Friedenthal, Kostlivy, and Hoskins have

² Sajous: "Internal Secretions," etc., vol. 1, p. 164, 1903.

sustained this view. I also concluded at the time, that the stage of the disease (not always reached because of recovery or death) which simulates myxœdema entailed also adrenal insufficiency, the conclusion submitted being: "The *asthenic* or *second stage* of exophthalmic goiter is due to exhaustion and functional insufficiency of the thyroid and adrenal glands, as a result of their prolonged overactivity during the *sthenic stage*." Here we have familiar clinical facts besides those of myxœdema, to sustain my position. Thus, referring to a case in which the skin had assumed "a peculiar bronze color," W. Macphar Semple³ expressed the opinion that there might "possibly be some more intimate connection between Graves's disease and Addison's disease than has been so far acknowledged"; Hirschlaff⁴ also reported a case due to fright in a girl, in which "there was extensive brownish pigmentation"; von Schrötter⁵ likewise observed a case in which "patches of dark-brown pigmentation were found over the entire body." In truth, we are dealing with a not-infrequent symptom of the disease, and recognized as such by classics, which clearly points to involvement of the adrenals.

We must not, however, as has been done, construe this as meaning that I "consider Graves's disease to be the result of excessive suprarenal activity, while myxœdema is due to the opposite condition, adrenal insufficiency." My position is specified in the two conclusions quoted above. Were the adrenals alone active in Graves's disease, its symptoms could not be distinguished from those evoked by adrenal overactivity, treated in the preceding chapter. Acting conjointly with the thyroid, however, the latter introduces factors that are directly traceable to it: the marked emaciation, for example, due to the rapid consumption of the body fat in this disease, as well as in certain adipose subjects treated with thyroid. I have pointed out the influence of the adrenals on oxidation. Now Magnus Levy, Salomon and also Steyrer found that the respiratory exchanges were increased from 50 to 80 per cent.^{5a} in Graves's disease.

Yet this does not mean that the influence of either organ may not predominate in proportion as its *relative* efficiency is

³ Semple: *Bristol Medico-Chirurgical Journal*, June, 1898.

⁴ Hirschlaff: *Zeit. f. klin. Med.*, Bd. xxxvi, H. 3-4, 1898.

⁵ Von Schrötter: *Medizinische Klinik*, April 5, 1908.

^{5a} Biedl: "Internal Secretory Organs," p. 98, 1913.

superior. Thus, Washburn,⁶ in a test of my contention that the adrenals take part in the process, writes: "Then we should expect high blood-pressure during a considerable part of the clinical course, that is, during the period of adrenal overactivity," and he gives 160, 170, 160, and 200 mm. Hg observed by him in four cases as proof of the correctness of my postulate. While this is perfectly true, and, as observed by Spiethoff,⁷ Morris and Edmunds,⁸ and others, there is a tendency toward a moderate rise of blood-pressure, the fact remains that in severe or advanced cases, contrary to what we should expect under the influence of a marked excess of adrenal secretion in the blood, there is a remarkable dilatation of the arteries of the entire organism with pulsation in the liver, spleen, capillaries, etc. Why should this occur? As we shall see, this is due to the action of the thyroid secretion, which, exaggerated, offsets that of the adrenal secretion.

And it is between the thyroid and the adrenals that the symptomatology finds its elements. The exaggerated secretory activity of both organs being synchronous, we have merely a correspondingly exaggerated expression of their normal functions. Thus, if the thyroid functions exceed those of the adrenals, we have vasodilation and a more or less marked depression of the blood-pressure, while if the adrenals predominate there is a rise of blood-pressure such as that observed by Washburn. The presence in the blood of an excess of adrenalin, in fact, has, since I urged the participation of the adrenals in Graves's disease, been demonstrated by Kraus and Friedenthal,^{8a} and also by A. Fraenkel.^{8b}

When fully developed, however, it appears to me that:—

Exophthalmic goiter is a constitutional disease due to excessive functional activity of the thyroparathyroid apparatus, and to the resulting dilatation of all arteries which the excess of thyroparathyroid secretion causes by producing excessive phosphorus oxidation (and elimination as P_2O_5) in all tissues, including the vascular muscles and the depressor nerve.

PATHOGENESIS AND SYMPTOMATOLOGY.—As recently stated by Biedl^{9c} "Graves's disease is the direct outcome of the flooding

Washburn: Wisconsin Medical Journal, March, 1907.

Spiethoff: Zentralblatt f. innere Med., Bd. xxii, S. 849, 1902.

Morris and Edmunds: Medical News, vol. lxxxvi, p. 62, 1905.

^a Kraus and Friedenthal, Berliner klin. Wochen., S. 1709, 1908.

^b A. Fraenkel: Archiv f. exp. Path. u. Pharm., June, 1909.

^c Biedl: "Internal Secretory Organs," p. 102, 1913.

of the organism with thyroid substances." But from my viewpoint, the clinical and therapeutic sides of the question render it advantageous to recognize three stages: 1, the *sthenic* or *erethic* stage, during which the overactive thyroparathyroid apparatus causes excessive sensitization of the phosphorus of all tissues to oxidation, and, therefore, abnormally active cellular metabolism; 2, the *transitional* stage, during which the overworked thyroid is beginning to be restrained by the gradual formation of sclerotic areas and atrophy and, 3, the *asthenic* or *myxædematous* stage, during which progressive fibrosis and atrophy increasingly inhibit the functions of the organ and finally cause the patient's death. The general vasodilation, though an important feature of the process, is incidental, and, as previously stated, subject to fluctuations.

STHENIC OR FIRST STAGE.—Under "hyperthyroidia" we have seen how clearly the excess of thyroiodase enhances all cellular activities—driving the cell to death, as it were. That the thyroid secretion and extracts increase tissue oxidation is generally recognized, but unlike the oxidation produced by an excess of adrenal secretion or extract there occurs, under the influence of the thyroid secretion, phosphoric acid metabolism and excretion, upon which Chittenden⁹ had laid stress. This is a feature of the action of thyroid products upon all phosphorus-containing structures, which stand out even more prominently in the clinical history of exophthalmic goiter than in the milder hyperthyroidia. The brain and nervous system are especially rich, as well known, in this element. The influence of the excessive thyroid activity, therefore, is shown by the greater agitation, restlessness (children being unusually irritable), hallucinations of sight and hearing, capriciousness or unusual gayety in the sthenic stage, which not infrequently includes also pseudo-hysteria, delirium, and even mania. Nervous disorders are so evident in the disease that the latter has been considered by many excellent authorities, including Putnam, as a neurosis. Tremors, especially marked in the upper extremities, but not infrequently involving even the muscles of the back and of the whole body—felt, as indicated by Maude, by placing the hands on the patient's shoulders while he is standing—are practically ubiquitous in

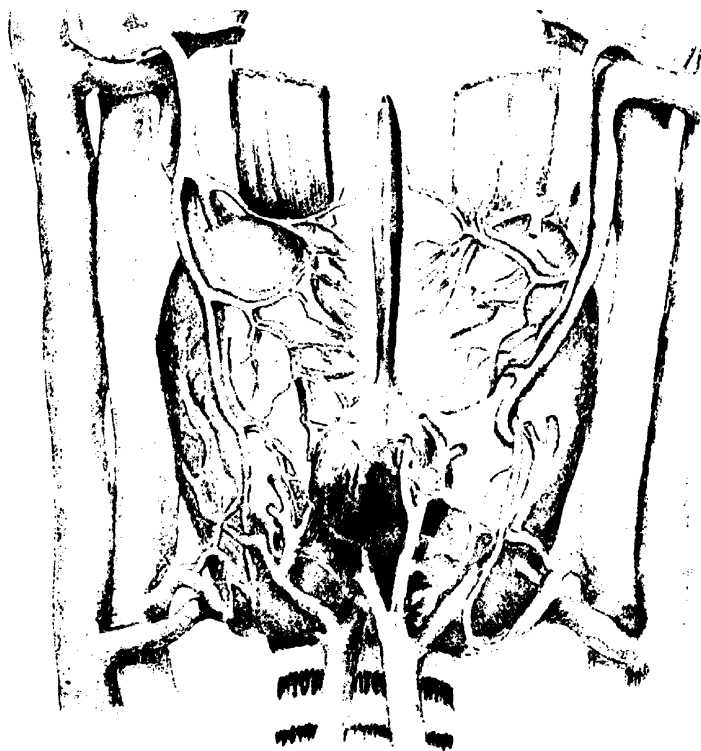
⁹ Chittenden: Trans. Cong. Amer. Phys. and Surg., vol. iv, p. 87, 1897.

these cases. Even the voice may become strident and tremulous. Choreic movements (which may replace tremors in children), local cramps, muscular spasms, and even epileptic convulsions are classic, and by no means rare, symptoms of the disease. They denote undue erethism in the cerebrospinal axis and the peripheral nerves, and explain the excessive excretion of P_2O_5 . The undue carbohydrate metabolism noted by Kraus, Ludwig, Chvostek, and others are but additional expressions of the same factor.

We cannot ascribe to the thyroid secretion *per se* any more than to the thyroid preparations in common use the powerful oxidizing power this denotes. It is here that "oxidizing ferment" of the blood, *i.e.*, the adrenal secretion converted into adrenoxidase, comes into play. Indeed, concomitantly, we find the evidences of increased oxidation. While a rise of temperature to 100° or 101° is the rule, some cases show a tendency to an acute febrile state, as observed by Gilman Thompson in a series of 70 cases, the fever reaching 104° F. and continuing sometimes several weeks, and recurring every now and then. Few diseases, in fact, furnish examples of such temperatures. In a case observed by Rendu,¹⁰ it reached in the course of one of these exacerbations 110° F., remaining two days between 107° and 110° F. The patients often complain bitterly of a sensation of warmth, of "burning flushes," especially when pruritus and sweating, both due to excessive metabolism in the skin and sweat-glands, are present. The increased demand for food and fluids betokens the intense rate of metabolism to which the tissues are subjected; indeed, polydipsia and boulimia are common. Yet, emaciation proceeds; the thyriodase, by increasing the vulnerability of the nucleus—also rich in phosphorus—of all fat cells to oxidation by the adrenoxidase, finally consumes all reserve fats; then follow nitrogenous tissues, whose cell nuclei are likewise rich in phosphorus.

The vascular phenomena, referred to above, and others they entail, are due, as stated in my definition, to this excessive oxidation and breaking down of all organic phosphorus, including that of vascular and nerve cells, and particularly Ludwig and Cyon's depressor nerve, which, as is well known, causes general vasodilation and a fall of the blood-pressure. Cyon found, moreover,

¹⁰ Rendu: Lyon médical, March 11, 1900.



VASCULAR SUPPLY OF THE THYROID GLAND.

that thyroid extracts excite the depressor nerve, an effect which the action of thyroid on the phosphorus of all cells explains.

The vascular dilatation may affect all the arteries of the body and be sufficiently marked to cause pulsation of all the large arterial trunks, most marked at the carotids and transmitted to the capillary system. It explains many, now obscure, phenomena that attend the disease. The tendency to hæmorrhages in the mucous membranes and skin is doubtless due to the fact that the dilated arterioles admit blood into the capillaries in excess of the volume the venules can readily carry off. Hence, the flushing of the skin, the hæmorrhagic areas in the mucous membranes, the epistaxis, the coffee-ground emesis, the subcutaneous extravasations of blood which, as in Popoff's case,¹¹ may attain huge dimensions, the telangiectasis, and, indeed, the gangrene occasionally witnessed. To the vasodilation may also be ascribed the œdemas often observed in the eyelids and legs, the fugitive swellings of the face, neck, arms, and joints, none of which are, of course, beneficially influenced by thyroid treatment. A distinct "whirr" may be heard in some cases over large vessels, as a result of the unusual volume of blood circulating through them.

The thyroid is, as a rule, only moderately enlarged, and its greatly dilated vessels likewise give rise to a distinct whirr under auscultation, while palpation elicits a thrill. During the first stage the goiter is relatively soft, and yields under pressure.

Exophthalmos, commonly the first sign (sometimes unilateral), belongs, when not merely apparent, *i.e.*, due to retraction of the eye-lids, to the same vasodilation of depressor origin, the vessels behind the eye-ball, especially of the retro-bulbar venous plexus, becoming greatly engorged. Here also we have dilatation of the arterioles, which admits an excess of blood into the tissues drained by this venous plexus. At first the exophthalmos fluctuates with the vascular dilatation, and may even be caused to disappear temporarily by pushing gently on the eye-balls. Later, no recession occurs owing to the local deposition of fat and connective tissue.

Stellwag's sign (in reality Dalrymple's,¹² who described it twenty years earlier), retraction of the lids, also finds its explanation in this vascular dilatation: the palpebral muscle

¹¹ Popoff: *Neurol. Centralblatt*, April 15, 1900.

¹² Dalrymple: *London Lancet*, May 26, 1849.

receiving an excess of arterial blood, it is unduly spastic, in keeping with other muscles of the body. This applies also to Graefe's sign: lagging of the upper lid when the eye-ball moves downward; its muscle being spastic, it cannot carry on its movements physiologically, that is to say, synchronously with those of the eye-ball. This spastic state may, in fact, be discerned by means of L. Napoleon Boston's sign¹³: The head being firmly braced, the patient is directed to follow as high as possible with his eyes the operator's hand, raised upward, starting from the level of the patient's chin about three feet away from his face, then brought down again. The upper lid will be noticed to follow the pupil downward a short distance, then to stop, when what the author terms a "spasm" occurs before it resumes its downward course. The dependence of both Stellwag's and von Graefe's signs upon so fluctuating a factor as the circulation is shown by the fact that they may vary from day to day and that they are not constant.

The tachycardia, one of the cardinal signs of the disease, in the light of these facts, is an expression of the febrile process, but only in part, for it persists even when the temperature is practically normal. The erethism of the central nervous system and of the nerves themselves, including the accelerator nerve, provoked by excessive oxidation in them, being taken into account, however, the abnormal pulse-rate finds its normal explanation even without the presence of a febrile state. Especially must this be the case in view of the fact that the myocardium itself is rendered hyperexcitable by the blood overladen with thyrioidase and adrenoxidase it receives. The cardiac symptoms of the disease, extreme irritability, distressing violent palpitations, with loud valvular sounds, especially marked at night, and even endocarditis, betoken the presence of such a condition of the entire cardiac mechanism. In children, in whom the disease develops rapidly, as a rule, the cardiac signs are often the first to appear.

The respiratory phenomena are closely allied to the cardiac, in that the respiratory muscles, including the diaphragm, are also rendered supersensitive by the excessive oxidation to which they are subjected by the blood, and the irritability of the nerves:

¹³ Boston: New York Medical Journal, August 17, 1907.

the phrenic, the respiratory nerve of Bell, the vagus, etc., they receive. The chest muscles being cramped, their excursions are restricted, and the air intake is correspondingly reduced. That the bronchial muscles are likewise contracted, abnormally reducing the caliber of the air channels, is probable. These two sources of diminished respiratory capacity suffice, it seems to me, to explain the sensations of suffocation or dyspnoea so often observed in these cases. As is the case with the tachycardia, this dyspnoea is subject to crises, during which the respirations become extremely rapid, sixty a minute, sometimes, as observed in two cases by Sharp.¹⁴ This observer noted that "opium had a marvelous action in slowing the respirations." As shown in the second volume, page 1272 of this work, opium, from my viewpoint, produces its effects by causing constriction of the arterioles—thus opposing precisely the muscular hyperæmia to which I ascribe the abnormal effects.

The alimentary canal is morbidly influenced by the same process, congestion and irritability of the gastric mucosa and muscular coat predisposing to emesis. A similar condition of the intestine is the underlying cause of diarrhoea. The liver, spleen, and lymph-glands are often found enlarged. The hyperæmia of all organs moreover gives rise to a general *malaise* or sensation of discomfort, the sensory terminals of all nerves being rendered irritable.

Various complications may occur, most distressing of which is ulceration of the cornea and loss of vision, through loss of protection of the lids and imperfect lachrymation and lubrication of the ocular surface.

Some cases of exophthalmic goiter recover spontaneously, though very gradually; others suddenly enter into a rapid downward course, which W. G. Thompson has compared to malignant endocarditis, for which disease it is frequently taken. A very rapid, tumultuous, and irregular heart action; hyperpyrexia; dyspnoea with labored breathing; vomiting; diarrhoea; hæmorrhages and ecchymoses; marked congestion and enlargement of the liver; delirium; stupor, and coma. In most cases, however, the typical symptoms of hyperthyroidia are replaced by a period of apparent quiescence—the transition stage—and then lapse

¹⁴ Sharp: London Lancet, June 27, 1903.

into those of hypothyroidia, the normal terminal morbid process of progressive exophthalmic goiter.

Transition Stage.—What appears to me to be entitled to this designation is a period in the course of the disease when there occurs apparently considerable improvement. The skin ceases to be abnormally moist, the heat flushes, the sensation of heat and the fever disappear, and the skin loses its suffused appearance, and may even become pale. The tremors and nervous irritability, and even the mental aberrations and emotionalism, are replaced by a gratifying placidity; the tachycardia greatly lessens, though reawakened by exertion. The emaciation tends also to disappear, and the patient, though weak, may even show a tendency to corpulence. On the whole, he appears to his surroundings greatly improved and even on a fair way to recovery.

If the goiter be examined with due care at this time, it will be found, at least in most instances, to have receded, and to have lost somewhat of its rounded shape. Its former softness still remains in some places, but in others nodular masses or bosses can readily be detected by passing a finger over the mass, and exerting slight pressure. The meaning of this is self-evident: the goiter is undergoing atrophy owing to the sclerotic areas with which it is now studded, and the transition stage is that period of the process during which the normal tissues, *i.e.*, what remains of them, are just able to sustain the metabolic equilibrium—although the latter is further compromised by the deficiency of cellular phosphorus following its excessive oxidation. The time finally arrives when the thyroid secretion produced is no longer sufficient and the case then enters into the:—

Asthenic or Myxœdematous State.—In this stage, reached, as previously stated, if cure or death does not occur early in the course of the disease, we witness the results of exhaustion of both the thyroid and the adrenals with fibrosis of the former. The recognition of this fact is important, for, while thyroid preparations are very harmful in the first stage, as many reported cases show, they may be useful when myxœdema has appeared. During the transition period the change is so rapid in some cases that certain symptoms of both exophthalmic goiter and myxœdema may occur together, the case lapsing ultimately into myxœdema. In textbooks its symptoms, unrecognized, are promiscuously

merged in with those of exophthalmic goiter. In a case witnessed by de Smet,¹⁵ the transition followed premature labor, the goiter alone remaining of the first disease. The exophthalmus may also persist.

The myxœdematous phenomena include most of those reviewed under Myxœdema, *i.e.*, the manifestations of hypothyroidia and hypoadrenia, and, as previously shown, the symptoms of impaired oxidation and metabolism these conditions entail. They are briefly: hypothermia, sensation of coldness, obesity with a non-pitting, rough, dry skin; supra-scapular swellings or pads, loss and coarseness of hair, brittleness and ridging of the nails, predisposition to onychia; various cutaneous disorders, leucoderma, scleroderma, vitiligo, brown pigmentation, etc.; mental torpor, depression, and irritability. There is intense weakness, especially of the legs, with occasionally a tendency to tabes-like paralysis, hemiplegia, or muscular atrophy, which may begin during the sthenic stage. There is a tendency to greater heart weakness and dilatation than in ordinary cases of myxœdema, owing probably to exhaustion of the cardiac muscle during the sthenic stage. If the patient is not carried off by some intercurrent disease, cachexia supervenes with a tendency to fainting spells and heart-failure, the usual cause of death.

ETIOLOGY.—In the first edition of this work (1903)¹⁶ I traced the primary cause of exophthalmic goiter to the pituitary body (the neural lobe), a nervous connection having been shown by Cyon, a physiologist, to exist between this organ and the thyroid, similar to that traced by myself between the pituitary body and the adrenals. The following year Salmon¹⁷ also concluded that the pituitary body was the seat of primary irritation, though his explanation of the process differed from mine. Briefly, from my viewpoint, the pituitary body contains the center of the thyroid and adrenals, and when certain toxics capable of irritating this center, such as the toxic wastes of pregnancy and menopause, various toxins, endotoxins, auto-toxins of intestinal origin, etc., occur in the blood during a prolonged period both these organs are unduly excited, and,

¹⁵ De Smet: *Le bulletin médical*, Oct. 24, 1906.

¹⁶ Sajous: "Internal Secretions," etc., 1st ed., p. 514, 1903, and p. 1861, 1907.

¹⁷ Salmon: *Clinique Moderne* (or *Clinical Med.*), Aug. 3, 1904.

their secretions being produced in excessive quantities, the disease is awakened.

That exophthalmic goiter occurs in persons predisposed to it by supersensitiveness of the central nervous system, as in hysterical, epileptic, and other neurotic subjects, is suggested by the frequency with which such disorders proceed or occur with the disease. Robinson¹⁸ and others have even gone so far as to consider it as a form of hysteria. Grandmaison,¹⁹ in a study of 32 cases, found hysteria in 19. Abadie ascribes the disease to irritation of whichever center governs the sympathetic vasodilator branches of the thyroidal vessels. Dana²⁰ vouchsafed a similar opinion. Von Gräfe, Köber, Charcot, and many other authorities have directed attention to the sympathetic in this connection, while Virchow, Trousseau, von Recklinghausen, and others have found lesions (which, from my viewpoint, need not necessarily occur) of the cervical sympathetic, whose branches supply the thyroid. Now, it is through the sympathetic that Cyon traced nerve-paths from the pituitary (the posterior lobe of which is a sympathetic structure, rich in chromaffin substance) to the thyroid, and, as I show in the second volume (pp. 982 *et seq.*), the pituitary contains, in all likelihood, the previously unidentified center of the sympathetic system.

One of the most evident indications of the influence of the waste accumulation on the genesis of the disease is shown in pregnancy. Richardson²¹ states that "in southern Italy it has long been the custom for the parent to measure the circumference of the daughter's neck before and after marriage, an increase in size being considered as an evidence of conception." Time has sanctioned this popular custom, various observers having shown that the thyroid becomes temporarily congested and enlarged under the influence of what Audebert²² terms, in describing a case in which exophthalmic goiter developed during the seventh month: the "usual symptoms of hepatic toxæmia." While exophthalmic goiter occurs rarely, the fact remains that it is but the exaggerated expression of a physiological process. Thus,

¹⁸ Robinson: "Etude sur les syndrome de Graves-Basedow considéré comme manifestation de l'hystérie," Paris, 1899.

¹⁹ Grandmaison: *Médecine moderne*, July 7, 1897.

²⁰ Dana: *New York Medical Journal*, June 14, 1902.

²¹ Richardson: "The Thyroid and Parathyroid Glands," p. 20, 1905.

²² Audebert: *Annales de gyn. et d'obstétrique*, Sept., 1906.

Lang,²³ in a series of 133 cases of pregnancy, found the thyroid enlarged in 108, the enlargement beginning about the fifth month. The thyroid ceased to increase in volume when thyroid gland was administered, and resumed its growth when the remedy was withdrawn.

That we are dealing with an antitoxic function having for its purpose the destruction of wastes of foetal and maternal origin, is suggested by the fact that the thyroid gland has long been credited with such a function. We have seen that my view that it increased the opsonic power of the blood has been sustained. Reid Hunt²⁴ found, moreover, that when mice were fed on small amounts of thyroid they showed marked resistance to poisoning by acetonitrile. The relationship of the pituitary body with the toxæmia of pregnancy is also shown by the observations of Comte,²⁵ that during pregnancy the pituitary body is also markedly enlarged, a fact confirmed by Launois and Mulon.²⁶ In a more recent paper Launois²⁷ reaffirms his former conclusion, stating that the anterior lobe (which, as I will show, page 1072, receives the toxics that awaken the impulses transmitted by the posterior lobe to the thyroid and adrenals) is, during pregnancy, "in a state of marked hyperactivity."

Another feature which points to the pathogenic rôle of intoxication is that, as stated by Ord and Mackenzie: "In districts where ordinary goiter prevails, the exophthalmic form is also met with." Grasset observed a similar coincidence in France, and Carter,²⁸ in England. The latter author states, moreover, that, while, in a certain valley in the West Riding, the inhabitants on one side of the river, who drink water from hills to the south, do not suffer from goiter, those on the other side of the river, who drink water from hills to the north, suffer a good deal from this growth. Moreover, it is from the latter, or goiter side, that cases of exophthalmic goiter are derived. This clearly suggests that the exophthalmic form is but a development of simple goiter. Indeed, referring to 3 cases of this "secondary"

²³ Lang: *Zeitsch. f. Geburts. u. Gyn.*, Bd. xl, S. 34, 1889.

²⁴ Hunt: *Jour. Amer. Med. Assoc.*, July 20, 1907.

²⁵ Comte: *Thèse de Doctorat*; Lausanne, 1898.

²⁶ Launois and Mulon: *Ann. de Gynécol. et d'Obstét.*, 2d série, vol. I, p. 2, 1904.

²⁷ Launois: *Thèse de la Faculté des Sciences de Paris*, 1904.

²⁸ Carter: *Edinburgh Medical Journal*, Oct., 1899.

type, Dean D. Lewis²⁹ writes: "In all these cases a history of goiter of some years' standing could be elicited. Two of these goiters were of the diffuse, colloid type, and one of the mixed type, partly parenchymatous, partly colloid. So far as I was able to determine, these goiters do not differ, histologically, from the simple colloid or parenchymatous goiter, unassociated with Basedow's symptom-complex." Goiter being due, according to prevailing views, to a telluric poison, its exophthalmic form must likewise be due to such a poison.

The relations between bacterial toxins, endotoxins and auto-toxins and the thyroid (with the latter organ considered as the source of one of the antitoxic constituents of the blood) also afford considerable evidence in this connection. Roger and Garnier³⁰ examined the thyroids of 33 cases which had died from scarlet fever, measles, diphtheria, small-pox, typhoid fever, cerebrospinal meningitis, and septic peritonitis, and found in all congestion and hypertrophy with increased secretion, and in two instances (variola and diphtheria) foci of parenchymatous hemorrhage. Marine and Lenhart³¹ also state that syphilis, typhoid fever, influenza, and articular rheumatism are frequently associated with or followed by thyroid hyperplasia. R. Abrahams³² reported 3 cases which developed in the course of active syphilis.

Closely associated with this class of causes is that described by W. H. Thomson,³³ *i.e.*, auto-intoxication from the alimentary canal due to imperfect gastro-intestinal digestion of nitrogenous foods. Treatment based on this view, in which meat was banished from the diet, and intestinal antiseptics were used, gave satisfactory results. While this view has been criticised, it is evident that, from my viewpoint, such poisons can, as well as any of the others referred to above, bring about the disease in predisposed subjects, by exciting the thyro-adrenal center, and thus cause an excessive production of thyroiodase and adrenoxidase. In a case reported by Aiken,³⁴ the disease began under ether anaesthesia and persisted six years.

²⁹ Lewis: *Surgery, Gynecology and Obstetrics*, Oct., 1906.

³⁰ Roger and Garnier: *La presse médicale*, April 19, 1899.

³¹ Marine and Lenhart: *Archives of Internal Medicine*, Nov., 1909.

³² Abrahams: *Philadelphia Medical Journal*, Feb. 9, 1901.

³³ Thomson: *Medical Record*, Jan. 13, 1900.

³⁴ Aiken: *Trans. Amer. Ophthal. Soc.*, 1897.

Excessive and prolonged exertion has also been known to produce the disease. Overwork is a generally recognized factor. Dauscher³⁵ reported a case which came on after climbing rapidly a steep mountain. Harland observed two instances which had appeared suddenly in soldiers who had been in action in the Boer War. Potain³⁶ called attention to the fact that violent anger, which has formed the starting point of exophthalmic goiter, awakens symptoms quite similar to this disease, protrusion of the eye-balls, trembling, violent palpitations, sweating, diarrhœa, psychical disturbances, etc. In all such cases wastes accumulate in the organism more rapidly than they can be hydrolyzed into eliminable products, and the disease is brought about precisely as in all the forms of toxæmia previously reviewed.

Fright and other violent emotions, which are relatively frequent causes of the disease, bring it on through a different, though kindred, process. Darwin and Sir Charles Bell, according to Carter,³⁷ describe a person in intense terror in the following words: "The heart beats quickly and violently, so that it palpitates or knocks against the ribs; there is trembling of all the muscles of the body; the eyes start forward, and the uncovered and protruding eye-balls are fixed on the object of terror; the skin breaks out into a cold and clammy sweat, and the face and neck are flushed or pallid; the intestines are affected." The resemblance of these phenomena to the symptoms of exophthalmic goiter is obvious. I refer, elsewhere in this volume, to the sympathetic center as the *sensorium commune*, in the sense that it bears the brunt of violent emotions, shocks, etc., as one of the most sensitive of all somatic centers. Now, as Carter correctly says, intense terror is "a condition in which the somatic nervous system is, for the time being, almost paralyzed." Traumatic shock, blows upon the head, etc., may produce the disease in a similar way, the violent concussion to which the sympathetic center is subjected, along with the other cerebral and basal centers, being the cause of the molecular disturbance. Delorme and Leniez,³⁸ for example, reported 2 cases in officers

³⁵ Dauscher: Wiener med. Presse, Feb. 17, 1899.

³⁶ Potain: Revue intern. de méd. et de chir., Oct. 10, 1895.

³⁷ Carter: Edinburgh Medical Journal, Oct., 1899.

³⁸ Delorme and Leniez: Le bulletin médical, July 20, 1910.

who had been thrown from their horses and had struck the pavement on their heads. There was in both cerebral concussion, followed two months later in the one, and one month later in the other, by exophthalmic goiter. They report a similar though less severe case in a soldier who had fallen from a roof, striking his head. Dyrenfurth^{38a} observed three cases due to accidents. The morbid effects of emotions, traumatic shock, etc., are attributable to a molecular disturbance of the sympathetic center,—which governs the caliber of the arterioles—*i.e.*, the thyro-adrenal center.

We have seen that poisons, by exciting the sympathetic thyro-adrenal center, so exaggerate the functional activity of the thyroid and adrenals that the characteristic action of an excess of thyroid secretion on phosphorus oxidation manifests itself, *viz.*, general vasodilation. With fright or any violent emotion capable of paralyzing the functions of the same center, we have general relaxation of all arterioles which the sympathetic center governs, the acute symptoms of fear being the expression of a temporary exacerbation of this vasodilation, *including those of the thyroid and adrenals*, and, therefore, an abnormal influx of arterial blood in these organs. This means for them, as shown by Claude Bernard in the salivary gland, a corresponding increase of functional activity. In the majority of such cases the resulting disturbances, though sometimes severe, are either recovered from as soon as the central molecular equilibrium is restored or, if this restoration does not occur, it may manifest itself by other disorders. If, however, heredity happens to predispose the victim of fright, shock, etc., to exophthalmic goiter, this disease is the one which develops; the circulation receiving an excess of thyroid secretion, the oxidation of cellular phosphorus becomes excessive, and the general vasodilation, the *deus ex machina* of the morbid process, is perpetuated.

The prevailing view that heredity influences greatly the development of the disease is based on a sound foundation. Among the examples may be cited the family referred to by Oesterreicher,³⁹ in which an hysterical woman's 10 children included 8 cases of exophthalmic goiter. One of these had 4

^{38a} Dyrenfurth: Deutsche med. Woch., Nov. 21, 1912.

³⁹ Oesterreicher: Cited by Chamberlain: "Maladie de Basedow," p. 13, Paris, 1894.

grandchildren, 3 of which suffered from the disease, while the fourth was hysterical. Hare⁴⁰ reported a case in a girl, whose great-grandmother and grandmother suffered from exophthalmic goiter, and whose great-aunt, aunt, and mother suffered from goiter, which increased with each pregnancy in the mother's case. Grober⁴¹ reported 4 cases of exophthalmic goiter in the same family, a brother, two sisters, and a niece. R. G. Curtin⁴² collected 40 cases of the disease in 15 families.

TREATMENT.—The great value of thyroid preparations in hypothyroidia suggests that they should prove harmful in the opposite condition, hyperthyroidia, and particularly in its most marked type, exophthalmic goiter. Indeed, many cases on record suggest that such is the case. But, in the light of the views submitted in the foregoing pages, the reason for these untoward effects is plain: they were due to the empirical use of these powerful agents and regardless of the stage of the disease and of dosage.

We have seen that exophthalmic goiter is divisible into three stages: the *erethic*, that during which there is excessive sensitization of the phosphorus of all tissues to oxidation and abnormally rapid cellular metabolism; the *transitional*, during which the overactive thyroid has undergone sufficient fibrosis to produce only such secretion as is needed by the body to carry on its functions, and the *myxœdematous*, during which advancing sclerosis of the gland is increasingly inhibiting its functions until these cease and death occurs. It is apparent that during the erethic stage the use of thyroid could but add fuel to the fire; that in the transitional it might prove useful to arrest the excessive activity of the thyroid, which is inducing sclerosis, by relieving it of part of its work, and finally that in the myxœdematous it should prove invaluable, as it does in myxœdema, as a life-saving measure. An even finer subdivision is necessary, however, one in which the primary cause of the disorder is taken into account, if satisfactory results are to be obtained. During the erethic stage, as a general rule, thyroid and iodine preparations are productive of serious harm. They enhance inordinately the oxidation of cellular phosphorus in all tissues and

⁴⁰ Hare: Intern. Medical Magazine, April, 1898.

⁴¹ Grober: Medizinische Klinik, Aug. 16, 1908.

⁴² Curtin: Trans. Amer. Climatol. Assoc., Sept., 1888.

increase, thereby, the general vaso-dilation, which, as I have shown, underlies all the major phenomena of the disease. In certain *mild* cases that are clearly due to a toxæmia of ovarian, uterine, or intestinal origin, thyroid is valuable (I have seen it cause complete retrogression of the goiter) in small doses, *i.e.*, 1 grain (0.066 Gm.) of the desiccated gland during each meal, with abstention from meats to decrease the formation of toxic wastes; but where the symptom-complex of the disease is present in its entirety, the aim should be to promote constriction of the arteries, and particularly of the arterioles which control the volume of arterial blood admitted into the organs, including the thyroid itself, the post-orbital vessels, and the cardiac muscle. It is because of this action, in my opinion, that Huchard obtained good results from ergot and hydrobromate of quinine. The latter drug has also been highly recommended in this country by Forchheimer. It may be given in 3-grain doses (0.198 Gm.) 3 times daily in capsules, increasing the dose until 5-grain doses (0.33 Gm.) are given. To prevent its unpleasant effects, which often occur promptly, and reduce the crethism of the cerebral centers (those of the pituitary in particular) I also give 20 grains (1.32 Gm.) of sodium bromide on retiring, adding 15 grains (0.99 Gm.) of chloral hydrate if the bromides do not counteract the insomnia.

Some highly nervous women, especially those who suffer from pseudo-hysteria, any preparation of quinine seems to increase discomfort. In these, the bromides at night, with chloral if necessary to counteract insomnia, should be supplemented by the use of phenacetin in the daytime, 5 grains (0.33 Gm.), gradually increasing the dose until 15 grains (0.99 Gm.) are taken three times daily. As stated above, the bromide reduces the pathogenic hypersensitiveness of the cerebral centers; the phenacetin maintains this action by causing constriction of the arterioles which supply them with blood—a common action of the coal-tar products (of which phenacetin is the safest), as stated in the second volume.⁴³

The favorable effects obtained by Rénon and Delille⁴⁴ with pituitary gland are explainable in much the same manner. In

⁴³ See vol. II, p. 1283 to 1293.

⁴⁴ Rénon and Delille: *Bull. gén. de thérap.*, May 8, 1907.

doses of $4\frac{1}{2}$ grains (0.3 Gm.) of the whole gland (ox), which they subsequently deemed advisable to increase to $7\frac{1}{2}$ grains (0.5 Gm.) in divided doses daily, they obtained marked improvement. Hallion and Carrion⁴⁵ then found experimentally that pituitary extracts "always produced their effects by raising the arterial tension," producing at the same time "an intense vasoconstrictor action upon the thyroid body." Briefly, we have here precisely the physiological action necessary—the vasoconstrictor power of the adrenal component of the pituitary gland superseding the vasodilator action of the thyroid, the underlying cause of the disease.

The morbid effects of the excessive oxidation of phosphorus to which the cellular elements are subjected require attention. The resulting exhaustion of the phosphorus in the muscular layer of the arteries aids powerfully the action of the depressor nerve in keeping the general vasodilation, including that of the thyroidal vessels, thus keeping up the disease. This phosphorus must, therefore, be replaced. Hence the value of sodium phosphate, noted long by Kocher, Trachewski, Vellesen (40 cases), and others, and of the glycono-phosphate of sodium in 20-grain doses three times daily, noted by M. Allen Starr—though none of these authors knew the *modus operandi* of these agents.

Of great importance to enhance the curative process is the free use of saline solution by enteroclysis and hypodermoclysis. The former, given at 108° F., sometimes suffices when, after clearing out the intestines by means of an enema, the solution, using a quart at a time, is retained sufficiently long to insure considerable absorption. If this is not the case, hypodermoclysis every other day, regulating the quantity according to the case, is indicated. By increasing markedly the osmotic properties and the viscosity of the blood, its toxicity and its exciting action on the thyro-adrenal center are greatly reduced, and the elimination of the pathogenic poisons by the kidneys and the intestinal tract is greatly enhanced.

The causative condition must be carefully sought and, if possible, removed. In cases due to pregnancy, menopause, and inadequate ovarian development, the disorder is mainly due to inability of the thyro-parathyroid apparatus to neutralize the

⁴⁵ Hallion and Carrion: Soc. de Thérap., March 13, 1907.

increasing tide of wastes the blood contains. The organ is abnormally stimulated, in the sense that its arterioles are widely opened to allow a vastly greater volume of arterial blood than usual to enter it, and it becomes enlarged. Here, thyroid preparations, starting with 1 grain (0.066 Gm.) *t.i.d.* of the dried gland, are of great value by compensating for the organ's deficiency. If the toxæmia is of intestinal origin, meats should be banished and free saline purgation—in addition to the measures advocated in the preceding two paragraphs—is indicated. Highly nervous or pseudo-hysterical cases are also helped by the bromide, phenacetin, and saline solution treatment, but rest in these cases and in those due to traumatic shock is of great importance. In fact, it must be borne in mind that exertion increases toxic waste formation, and, therefore, the asset of pathogenic poisons, and that rest is always indicated.

Various sera obtained from animals deprived of their thyroid: Ballet and Enriquez's dog serum, Möbius's sheep serum, or "antithyroidin," Rogers and Beebe's serum, obtained from rabbits or sheep inoculated with extracts of exophthalmic goiter, are all of value in that they are all antitoxic substances which aid the blood in neutralizing the pathogenic poisons. This applies also to Lanz's results with the milk of thyroidectomized goats' milk, which gives the same reactions as blood-serum in so far as its antitoxic constituents are concerned.

During the *transitional* stage the treatment depends entirely upon the progress made by the atrophic process. As a rule, however, signs of myxœdema are already present; in that case thyroid preparations are indicated, as they are during the *myxœdematous* stage. The latter is virtually a case of myxœdema and requires the measures recommended for that disease (*q.v.*). In both these stages, however, there is a marked tendency to cardiac failure, and digitalis or strophanthus are precious adjuvants.

When medicinal treatment fails, surgical measures are indicated: partial thyroidectomy or, as frequently done by the Mayo brothers, ligation of the thyroid arteries—a measure quite in keeping with the aim of the treatment detailed above. The X-ray applied only to the gland has also been recommended by Rave, Simon and Berger Schwaab.⁴⁶

⁴⁶ Berger and Schwaab: Cited by J. H. Jacobson, *Annals of Surgery*, March, 1913.

CHAPTER VI.

THE ADRENAL SYSTEM AND FUNCTIONAL ACTIVITY.

By "adrenal system," I mean a functional union of the three organs studied so far, viz., the pituitary body, the adrenals, and the thyroparathyroid apparatus, the first-named organ containing, as previously stated, the governing or co-ordinating center of the two others. The importance of this union will assert itself when we consider such diseases as acromegaly, which, though due primarily to a lesion of the pituitary, manifest themselves through their influence upon the adrenals and the thyroparathyroid apparatus.

To make this and other questions intelligible, however, it is necessary to show that what I have termed *adrenoxidase* (the oxidizing substance of adrenal origin) circulates in all organs—in conjunction, of course, with the thyroparathyroid secretion, though the latter will not be mentioned, to avoid confusion. Even the nervous system, we shall see, is traversed by adrenoxidase, thus bringing the neuron itself within the field of the general circulation.

ADRENOXIDASE AND THE MOTOR NERVES IN THEIR RELATION TO MUSCULAR CONTRACTION.

The skeletal muscles stand apart in respect to vasomotor functions. The sympathetic system supplies nerves to unstriped muscular fibers elsewhere, and yet this system is not known to extend to the extremities. Again, vasoconstrictors and vasodilators are said to accompany the larger nerve-bundles,—the sciatic, for instance; but a survey of the field distinctly shows that the evidence as to the existence of separate vasoconstrictors is purely inferential. Since the sympathetic nerve does not appear to send subdivisions to this class of muscles, the association of constrictors of another source introduces an element of confusion, not only as regards the peripheral structures themselves, but particularly in respect to the central origin of the two systems classed under the one single term of "vaso-

motors." As it is impossible to proceed without clearing this question, we will first ascertain whether the prevailing views as to the physiology of the circulation in the muscular system may not, in the light of my own conceptions, be subject to change.

ADRENOXIDASE AND MYOSINOGEN.—In the production of muscular contraction a nerve-impulse is of course transmitted to the muscular elements; but how are this impulse and the resulting contraction related to the functions of the blood itself? This question is suggested by the rôle I have assigned to the oxidizing substance or adrenoxidase.

Stewart¹ refers to the thermal phenomena of muscular contraction as follows: "When a muscle contracts, its temperature rises; the production of heat in it is increased. This is most distinct when the muscle is tetanized, but has also been proved for single contractions. The change of temperature can be detected by a delicate mercury- or air- thermometer; and, indeed, a thermometer thrust among the thigh-muscles of a dog may rise as much as 1° to 2° C. when the muscles are thrown *into tetanus*." That tetanus is a phenomenon of hyperoxidation through suprarenal overactivity we have suggested when studying the action of drugs. This affords a first clue: If the plasma contains an oxidizing substance, the chemical changes in muscular tissue during contraction—*i.e.*, absorption of oxygen, increased production of carbon dioxide, change of reaction from neutral or alkaline to acid, and finally the formation of sarcolactic acid—clearly suggest that the contractile process and the mechanical energy utilized may be due to an increased supply of oxygen through the agency of the oxidizing substance. Indeed, Kronecker has shown that "the injection of arterial blood or even of an oxidizing agent like potassium permanganate into the vessels of an exhausted muscle also causes restoration." If an agency so remote in composition from the normal organic fluids can restore merely through its oxidizing power an exhausted muscle, so eminently physiological a fluid as the blood-plasma, charged with oxygen *in loose combination*, must surely possess correspondingly active properties. Indeed, the link seems to

¹ Stewart: "Manual of Physiology," p. 598.

be a strong one if the full meaning of the following sentence from Foster's "Physiology" (sixth edition) is gathered: "We might compare a living muscle to a number of fine, transparent, membranous tubes *containing blood-plasma*." If we also recall the fact that capillaries do not possess contractile fibers and that arterioles represent the ultimate subdivision to which vasomotor nerves are distributed, it becomes clear that we have all the mechanical elements necessary to account for some unexplained phenomena that attend muscular contraction. An impulse capable of causing a change of caliber of a peripheral arteriole would thus suddenly admit more arterial blood—*i.e.*, more oxygen-laden plasma—into the "fine, transparent, membranous tubes," and contraction, an inherent property of muscular tissue, would follow.

The prevailing views as to the nature of the process through which the mechanical energy utilized during muscular activity cause contraction or retraction may be illustrated by selections from Professor Foster's text. Referring to the chemical analogy between the axis-cylinder and muscle-tissue, he says: "We have no satisfactory evidence that in a nerve even repeated nervous impulses can give rise to an acid reaction" . . . "nor have we satisfactory evidence that the progress of a nervous impulse is accompanied by any setting free of energy in the form of heat." In the summary, referring to the terminal phenomena, he remarks: "This muscle-impulse, of which we know hardly more than that it is marked by a current of action, travels from each end-plate in both directions to the end of the fiber, where it appears to be lost; at all events, we do not know what becomes of it. As this impulse-wave, whose development takes place entirely within the latent period, leaves the end-plate, it is *followed* by an explosive decomposition of material, leading to a discharge of carbonic acid, to the appearance of some substance or substances, with an acid reaction, and probably of other unknown things, with a considerable development of heat. This explosive decomposition gives rise to the visible contraction-wave, which travels behind the invisible muscle-impulse at about the same rate, but with a vastly increased wave-length. The fiber, as the wave passes over it, swells and shortens, and thus brings its two

ends nearer together. When repeated shocks are given, wave follows wave of nervous impulse, muscle-impulse, and visible contraction; but the last do not keep distinct; they are fused into the continued shortening which we call tetanus."

The last word, "tetanus," stands as the highest expression of a rapid succession of nervous impulses; but, viewed from my standpoint, this succession of impulses can as readily produce successive variations of vascular caliber, and give rise to precisely the phenomena witnessed, by admitting the oxidizing substance of the blood-plasma into the fine, "membranous tubes." The shock experienced when the current is turned "on" or "off" further suggests that the latter process is the true one. "The mere passage of a constant current of uniform intensity through a nerve does not, under any circumstances," says Professor Foster, "act as a stimulus generating a nervous impulse; such an impulse is only set up when the current either falls into or is shut off from the nerve. It is the *entrance* or the *exit* of the current, and not the continuance of the current, which is the stimulus." . . . "It is the sudden change from one condition to another, and not the condition itself, which causes the nervous impulse."²

The confusion that attends prevailing views as to the manner in which muscular tissue is physiologically caused to contract is readily accounted for when, in the light of the newer conceptions outlined in the last chapter, we analytically dissociate the various causal elements of muscular activity. Indeed, we have seen that various phenomena ascribed to the sympathetic system belonged to the domain of the adrenals *i.e.*, to what I have termed the adrenal system; we are again brought to realize that in all organs certain functions must likewise, and for the same reasons, be disconnected from others as regards their immediate purpose in the tissues. Thus, the fact that the muscle-impulse, which "travels from each end-plate in both directions to the end of the fiber, where it appears to be lost," is at present considered as an inherent, though causal, element of the "explosive decomposition of material, etc.," through its activity as a physiological stimulus.

² All italics are my own.

But if we can separate these elements of the process into two distinct parts, viz.: (1) a nervous impulse to the muscular elements themselves, and (2) a simultaneous change in the caliber of the local arterioles, the fact that as the impulse leaves the end-plate "it is followed by an explosive decomposition of material, leading a discharge of carbonic acid," will stand as the only result to be expected. Such a division becomes necessary in the light of my conception of the process.

While the nerve-impulses only have for their purpose to excite and govern contraction, the blood—*i.e.*, the blood-plasma mainly—through its oxidizing substance becomes the factor through which the chemical process to which contractile work is due is suddenly awakened. A feature of this conception upon which particular stress must be laid—since it applies to all organs—is that it dissociates from the oxidation process *per se* a stimulus which does not belong to it and which, therefore, introduces elements of confusion. "We cannot tell," says Stewart, "in what the 'natural' or 'physiological' stimulus to muscular contraction in the intact body really consists, nor how it differs from artificial stimuli." Relieved of this autonomous agency the organic physico-chemical processes enter within the limits of exact investigation.

Oxygen in other fields of thermochemistry is known to constitute the reactionary agent through which "explosive decomposition" is awakened and sustained. That it fulfills the same rôle in this connection, some complex organic compound in the muscular fibers constituting the primary source of energy or fuel, is probable. Under these circumstances the passive "irritability" of a living muscle would be maintained by a continuous reaction in which the reagents would be these compounds—*i.e.*, hydrocarbons—and the oxygen held in loose combination in the blood, particularly the blood-plasma, which penetrates the contractile elements themselves. This *irritability* would then become abruptly converted into *contractility* when the blood-supply—*i.e.*, the plasma in the contractile fibers—would be increased through the arrival of more oxygen.

Considerable familiar evidence besides that already adduced is available in support of this conception of the general physiology of muscle-tissue. Although continuous muscular

contractility is generally thought to be associated with nerve-impulse, destruction of all nervous connection with a muscle does not cause it to lose its excitability. Its inherent property in this particular is shown by the fact that, although the apex of the heart contains no nerve or nerve-cells, it nevertheless responds to stimulation. Even when detached from the body, muscles preserve their contractility for a time under suitable conditions. This would appear to eliminate the need of further energy to account for the phenomena witnessed; but the contrary is the case, since it shows why muscular tissue, owing to its inherent irritability, responds to various stimuli: vital, electrical, physico-chemical, and mechanical. Electricity, we know, acts as a powerful stimulus, but heat alone acts in precisely the same manner if the temperature is adequate and is raised rapidly; marked contraction may thus be caused when 30° C. is reached, and violent activity induced before the muscle is heated to 45 degrees. Chemical stimuli will produce the same effect, provided the reaction induced occurs with sufficient rapidity.

That the nervous impulse is not the source of mechanical energy utilized under these circumstances, is shown by the fact that a chemical stimulus applied to a nerve, ammonia, for instance, will not stimulate it though it will excite the muscle; various acids, hydrochloric, acetic, etc., will give rise to the same phenomena. "Certain poisons (curare) cause the motor nerves to become completely incapable of action," says M. Duval, "and, therefore, incapable of transmitting irritation to a muscle; nevertheless, under these circumstances, the excited muscle can directly pass from the state of rest to that of activity (Claude Bernard, Kölliker); the ultimate and fine nervous ramifications that they contain take no part in this *irritability*, since the poisons referred to kill mainly the intramuscular endings of the nerves (Vulpian). A motor nerve separated from the cerebro-spinal axis loses, after four days, all excitability; the muscle, on the contrary, previously innervated by this nerve remains directly excitable more than three months (Longet)."

That muscle is directly and independently excitable by a large number of stimuli is evident; that oxygen should,

through exacerbations of a continuous physico-chemical reaction of which its tissues are the seat while in the passive state, be able suddenly to awaken the active state is as clear. When the muscle is in the passive state, the transformation of energy incident upon the continuous reaction manifests itself as heat; while, when it is active, it manifests itself as greater heat *plus* mechanical work. Armand Gautier has ascertained that a working muscle took up *nine times more blood than a resting one*, and that the ratio of carbonic acid given off by it or transmitted to the venous blood was nearly one hundred times greater. This raises the question as to whether the conversion of chemical energy into the mechanical work upon which contraction depends must first be transformed into heat energy. A study of this question by Professor Gautier, based on Carnot's investigations, showed that, just as in a voltaic cell in which the chemical potential at once appears under the form of electricity without passing through the intermediate state of heat, so can intramuscular chemical energy become directly transformed into work. Indeed, he found that 65° C. (149° F.) would represent the final temperature of an active muscle, were it otherwise, and reached the conclusion that "a muscle contracts and works owing to a direct transformation of the chemical potential into elastic tension, without ever requiring the intervention of the heat which theoretically accounts for internal combustions."

These facts seem to me to warrant the deductions:—

1. *That the mechanical energy utilized by living voluntary muscles in the passive state is converted chemical energy, the result of a reaction in the muscular contractile elements during which various compounds, mainly hydrocarbons, are oxidized.*

2. *That active muscular work is the result of an exacerbation of the activity of this mechanical process, attended with a direct transformation of the passive potential: i.e., irritability, into the active potential: i.e., contractility.*

The suggestion that the reaction occurs in the living contractile elements themselves cannot, for obvious reasons, be demonstrated experimentally. But if we associate Foster's comparison of a living muscle to "a number of fine, transparent, membranous tubes containing blood-plasma" with my

conception of the nature of blood-plasma as an excipient for an oxidizing agent of adreno-pulmonary origin, on the one side, and, on the other, recall the view of Englemann, that a fluid substance passes from the bright bands of the fiber—*i.e.*, the interstitial disks—into the dark bands—*i.e.*, the contractile disks,—the intimate process would be as follows: *The hydrocarbon compounds would occupy the contractile disks, while the oxidizing substance would fill the interstitial disks, and on the proportion of the latter entering the contractile disks would depend the activity of the oxidation process and the degree of contraction.*

Further evidence that the general process outlined prevails may be obtained by tracing the identity of myosin: the substance found in the muscles after death. "While dead muscle contains myosin, albumin and other proteids, extractives, and certain insoluble matters, together with gelatinous and other substances not referable to the muscle-substance itself," says Professor Foster, "living muscle *contains no myosin*,³ but some substance or substances which bear somewhat the same relation to myosin that the antecedents of fibrin do to fibrin, and which give rise to myosin upon the death of the muscle. There are, indeed, reasons for thinking that the myosin arises from the conversion of a *previously existing body which may be called myosinogen*, and that the conversion takes place, or may take place, by the action of a special ferment, the conversion of myosinogen into myosin being very analogous to the conversion of fibrinogen into fibrin. We may, in fact, speak of *rigor mortis* as characterized by a coagulation of the *muscle-plasma* comparable to the coagulation of blood-plasma, but differing from it inasmuch as the product is not fibrin, but myosin. The rigidity, the loss of suppleness, and the diminished translucency appear to be, at all events, largely, though probably not wholly, due to the change from the *fluid plasma* to the *solid myosin*. We might compare a living muscle to a number of fine transparent membranous tubes containing *blood-plasma*. When this blood-plasma entered into the 'jelly' stage of coagulation, the system of tubes would present many of the phenomena of *rigor mortis*. They would lose much of

³ All italics are our own.

their suppleness and translucency, and acquire a certain amount of rigidity. There is, however, one very marked and important difference between the *rigor mortis* of muscle and the coagulation of blood. Blood during its coagulation undergoes a slight change only in its reaction; but muscle during the onset of *rigor mortis* becomes distinctly acid."

If myosinogen were the precursor of the myosin of *rigor mortis*, what would its composition probably be and how would it become metamorphosed into myosin?

I have submitted the data sustaining my view as to the existence of the oxidizing principle, and have referred to it as a body derived from the suprarenal glands, which, in passing through the lungs, entered into loose combination with oxygen. The labors of Schmiedeberg, Salkowsky, Jaquet, Abelous and Biarnés were quoted to show that such a principle had also been found by chemical methods, though its origin remained unknown to them.

If combustion of products of nuclein metabolism in the blood-plasma, through the presence therein of oxidizing substance, can produce uric acid, it seems reasonable to conclude that, if this same substance is also present in myosinogen, we should find evidence of a similar action. Not only is this the case, but the same products of metabolism are found in muscle-serum: the liquid portion of muscle-plasma obtained by rubbing up and expressing fresh muscle. Though obtained only in very small quantities, the purin bases, creatin, xanthin, hypoxanthin, and creatinin, are always found in addition to their end-product, uric acid. Phosphoric acid—a waste-product derived mainly from the catabolism of nerve tissues—is another link between muscular plasma and that of the general blood-stream. Of course, these various bodies should not be considered as elements of muscular activity. Their history indicates that, along with other albuminoids found, they are mere passive hosts of the muscular plasma as waste-products of muscular *tissue*-metabolism, destined to be converted here, as elsewhere in the organism, into harmless bodies, acids or others.

The active constituents of myosinogen, as far as muscular irritability and contractility are concerned, must be of another

kind, and are perhaps specific to muscle. Especially must this be the case since it possesses, we have seen, a special physical attribute: *i.e.*, the direct conversion of chemical energy into mechanical work, without involving the *corresponding* evolution of heat which oxidation elsewhere in the organism engenders. The word "corresponding" is used because we must not lose sight of the fact that considerable heat is produced during muscular contraction, and, indeed, that it is subject to marked variations under the influence of fatigue, tension, the state of the blood, the work done, etc. Yet the heat evolved is not commensurate with the muscular work done, and if we deduct from the heat potential actually produced that which intramuscular combustion of waste-products incident upon increased exertion entails—an unproductive factor as regards work—the need of the direct conversion of chemical energy into mechanical work—*i.e.*, contraction of the muscle—will appear.

One of the constituents of myosinogen giving this body Foster's interpretation (page 240) must be glycogen, since it is the constituent of muscle which diminishes during activity, while it accumulates during rest. Glycogen was shown by Claude Bernard in 1848 to be formed in the liver-cells from food, especially from sugars and starches, derived in turn from glucose: one of the products of digestion. Herbivorous animals, such as oxen, horses, etc.,—*i.e.*, those that only feed upon substances that contain these hydrocarbons,—are obviously endowed with great muscular power. It is evident, therefore, that the source of the energy to be ultimately transformed into mechanical work must be stored in these vegetable substances to a very great extent. Glycogen may not, however, migrate as such toward the muscular elements—since it would undergo oxidation in the blood; it is thought to be retransformed into glucose by a ferment and distributed as such to the muscular tissue, where it is again dehydrated ($C_6H_{12}O_6 - H_2O = C_6H_{10}O_5$) into glycogen, ready for functional use. This question will be studied later on.

Outside the organism lactic acid is known to be a product of fermentation of glucose, dextrin, and glycogen; hence the conclusion that *sarcolactic* acid is formed during muscular contraction. According to prevailing views, however, the evidence

tends to show that such is not the case, because sarcolactic acid is produced during progressive *rigor mortis*, precisely as it is during muscular contraction. If, however, the process is interpreted from my standpoint, including the presence of an oxidizing principle in the muscle-plasma,—i.e., the myosinogen,—this negatory evidence is eliminated. According to classic doctrines, the nervous impulse is a *direct* initial factor of muscular contraction, whereas from my standpoint it is an indirect initial factor, an excess of oxygen being the incitor of contraction. The continuation of oxidation during the progress of *rigor mortis*, therefore, becomes a normal outcome of the *post-mortem* vascular dilation, the remaining oxygen entering into combination with the hydrocarbons present, as long as the myosinogen is sufficiently liquid to permit of it: i.e., before it has assumed the state of myosin.

Considered from this point of view the many mooted features of the process appear—it seems to me—under their proper light. Glycogen is absolutely known, first, to diminish during muscular contraction; second, to accumulate during rest; third, to decrease rapidly when an unfed animal is made to work. Notwithstanding these established facts, it is deemed inadequate, as judged from the analysis of *dead* muscle, to quantitatively satisfy the needs of the process. With oxygen as the initial factor it becomes clear that dead muscle only shows the residue of the combustion that has gone on during the progress of *rigor mortis*, and that the glycogen ratio should therefore include that of the sarcolactic acid,—to say nothing of other products of combustion that may be present,—which would bring the proportion of glycogen to a much higher figure than analyses under present conditions furnish.

Can we say, however, that glycogen alone satisfies the needs of the process? The fact that the most powerful of our domestic animals—oxen, horses, camels, elephants, etc.—are all herbivorous would suggest that such is the case. Again, it is the one constituent that is positively known to diminish during work and to accumulate during rest. All other sources, even fats, which are probably entitled to a place among the sources of muscular energy, have only been theoretically associated with muscular work, while the fact that the amount

of urea is not materially increased during muscular exertion tends to eliminate the proteids. Muscles from which glycogen is absent are stated to respond to stimulus; but the inherent irritability of muscle-tissue readily accounts for this. On the whole, experimental evidence, if considered in the light of the views herein advanced, tends to show that *glycogen is the main constituent of myosinogen with which the oxygen of the blood-plasma combines to incite contraction.*

The absence of free oxygen in muscle has been adduced as evidence to show that the carbonic acid evolved could not be formed by direct combustion. It becomes clear that if the oxygen is used up to the last—to such a degree that a muscle will absorb oxygen from the surrounding atmosphere—none will be obtained from its tissues, even with the air-pump. The transition of a muscle from its normal neutral reaction to an intensely acid one when the *rigor mortis* is fully established, is also accounted for by the oxidation of glycogen. Prolonged tetanus likewise causes acidity of the muscle; we have seen that this is due to excessive suprarenal activity: *i.e.*, to hyper-oxidation.

This subject is of such importance that we deem it advisable to meet each mooted point as presented by Professor Foster precisely as if the problems were placed before us for solution:—

1. "At the outset of *rigor mortis* there is a very large and sudden increase in the production of carbonic acid: in fact, an outburst, as it were, of that gas."

The onset of *rigor mortis* also represents the moment when vascular tonic contractions cease; the blood-vessels being suddenly dilated, a correspondingly great amount of oxidizing substance is as suddenly brought into contact with the energy-holding substances in the myosinogen, and an outburst of carbonic acid ensues.

2. "The increased production of carbonic acid during *rigor mortis* is not accompanied by a corresponding increase in the consumption of oxygen."

This conclusion, based on the consumption of oxygen in which the dead experimental animal is placed, does not take into account the oxygen stored in the animal's blood-plasma.

As shown in the first answer, the oxidizing substance in the latter is fully able to give rise to the production of the carbonic acid observed.

3. "A muscle (of a frog, for instance) contains in itself no free or loosely attached oxygen; when subjected to the action of a mercurial air-pump it gives off no oxygen to a vacuum, offering, in this respect, a marked contrast to blood."

A detached muscle is, as far as its vascular elements are concerned, similar to a muscle in which *rigor mortis* has begun. Its oxygen is not in sufficiently loose combination to yield to the dissociating action of the pump when stored in myosinogen, owing to its affinity for various constituents of the latter. While in *extra corpore* blood the oxidizing principle of the plasma might yield its oxygen *in vacuo*, it is probable that it will not, judging from recorded data, though it will do so to salicylic aldehyde, benzol, and benzilic alcohol, as shown by Schmiedeberg, Jaquet, Salkowsky, Abelous and Biarnès.

4. "When placed in an atmosphere free from oxygen it will not only continue to give off carbonic acid while it remains alive, but will also exhibit at the onset of *rigor mortis* the same increased production of carbonic acid that is shown by a muscle placed in an atmosphere containing oxygen. It is obvious in such a case that carbonic acid does not arise from the direct oxidation of the muscle-substance, for there is no oxygen present *at the time* to carry on oxidation."

The oxidizing substance when brought into contact with the myosinogen gives rise to an intramuscular reaction: one which, therefore, may continue in any atmosphere whether the latter contains oxygen or not.

Professor Foster then summarizes prevailing views as to this subdivision of the general subject, as follows: "We are driven to suppose that during *rigor mortis*, some complex body containing in itself ready-formed carbonic acid, so to speak, is split up, and thus carbonic acid is set free, the process of oxidation by which that carbonic acid was formed out of the carbon-holding constituents of the muscle having taken place at some anterior date."

The process appears to me to be fully accounted for as follows: *The presence of the oxidizing principle which the supra-*

renal glands indirectly furnish to the blood-plasma accounts for the phenomena witnessed. The abrupt increase in the production of carbonic acid after death is due to the sudden relaxation of the normal tonic vascular contraction incident upon the lethal state and to the equally sudden onslaught of oxidizing substance upon the myosinogen thus induced. Myosinogen becomes myosin when the supply of oxidizing substance ceases.

But can functional activity be maintained in an organ merely by an increase of the local blood-supply? That such is the case may be shown by means of one of Claude Bernard's experiments,—that in which he demonstrated the existence of vasodilator nerves. Having severed the chorda tympani,—a branch of the facial distributed to the submaxillary gland,—he found that, when the peripheral segment of the cut nerve—that leading to the gland—was electrically stimulated, its normal function became manifest. Mathias Duval described the phenomena that immediately ensue as follows: “While the salivary secretion is thus increased, the blood-vessels of the gland are seen to become greatly enlarged; previously invisible arterioles become red and turgescient. If the main trunk of the gland is exposed, it is seen to increase in size, while its contained blood, *blackish before the experiment, becomes as red as arterial blood* the moment the chorda tympani is stimulated; indeed, if the vein is cut, the blood may be seen to flow in rhythmic jets, as it does from an artery, while it merely drools out when the gland is in the state of rest: *i.e.*, when the chorda tympani is not excited.”

The organ selected for the illustration, the submaxillary gland, is particularly advantageous for the purpose, because its vasodilator nerve, the chorda tympani, is isolated from the vasoconstrictor branch of the sympathetic, also distributed to the gland: a feature of importance. Again, it is evident that function occurs without the active participation of the nerve-impulse *per se*, such as that associated with a “motor” nerve. We have, in Professor Duval's presentation of the process, an exact description of the mechanism of active function. There is not only increase of blood, but increase of energizing blood: *i.e.*, blood that is not allowed to become venous *in situ*. The carbonic acid evolved must at once be removed; hence the

rapid flow; while the veins are for the time being, as long as active functions continue, transformed into arterial channels. Briefly, more arterial blood means more work. As we shall see later on, this is the only process through which the potential of any organ—i.e., its latent power to do work—is maintained and its functional activity awakened when required. Whether the structure involved be muscular, hepatic, gastric, renal, cerebral, splenic, etc., the exciting factor of activity is always—shall we say *blood*? No; all this evidence shows that *the oxidizing substance (adrenoxidase) is the main factor of all functional processes, and that the red corpuscles are but carriers of this substance, which they deal out to the plasma to sustain its efficiency as an oxidizing body.* We have seen that Salkowski was also led, but by chemical methods, to deny the red corpuscles the all-important rôle now ascribed to them.

THE MOTOR NERVES AND THEIR RÔLE IN MUSCULAR CONTRACTION.—We must now transfer our attention to the “vasoconstrictor” side of the question. The sciatic nerve is thought to be supplied with vasodilator and vasoconstrictor fibers. Division of this nerve causes the usual widening of the arteries, while electrical stimulation of the peripheral nerve-end causes contraction of the dilated arteries. This coincides with the experimental results of section of the cervical sympathetic, the splanchnic, etc., already given. “But sometimes a different result is obtained,” says Foster, “on stimulating the divided sciatic nerve: the vessels of the foot are not restricted, but dilated—perhaps widely dilated”: a phenomenon which leads him to conclude “that the sciatic nerve (and the same holds good for the brachial plexus) contains both vasoconstrictor and vasodilator fibers,” and to interpret the varying results as due “to variations in the *relative irritability* of the two sets of fibers.”⁴ These remarks are only intended by their author to convey, not a personal conclusion, but an inferential deduction based on what testimony the experiment referred to affords as to the existence, in the sciatic and brachial plexuses, of both constrictor and dilator fibers. It is the value of the testimony itself, and not the author’s deduction, therefore, that we are analyzing.

⁴ The italics are my own.

A query that normally suggests itself is the following: What is the experimental value of the current for the determination of the specific function of *any* nerve when its *relative* irritability is a sufficiently prominent factor to cause it to indicate, under the influence of this current, one function at one time and the opposite function the next? Evidently the variation in irritability must mean either—as is the case with the nerves of the parotid gland—that the antagonistic nerves are directly connected or juxtaposed or that one is sufficiently metamorphosed organically as to modify its conductivity. Framed in this manner, the query meets with a ready response: Inasmuch as vasoconstrictor and vasodilator nerves *accompany* the sciatic nerve, they become *common* conductors when the circuit is closed, and any indication furnished, therefore, is of no scientific value.

There is another possible explanation, however, viz.: Either one of the dilator or constrictor nerves may be absent in the structures supplied by the sciatic and the brachial plexuses. In other words, skeletal muscles may only be supplied with one of these nerves. Yet there is no experimental difference between these and other structures of distribution; thus, section causes vasodilation, while stimulation gives rise to constriction of the vessels, and, if either of the vasomotor nerves is not supplied to these structures, their motor nerves must fulfill the rôle of the absent system. I could readily enough state, after eliminating the only evidence in favor of the existence of vasoconstrictors, that there are none in striated muscles, all the positive evidence pointing only to the existence of vasodilators. But we must not lose sight of the fact that I have interpreted the experimental evidence at our disposal in a different manner, and that my own views must also be shown to be in accord with this evidence, if they are to merit confidence.

From my standpoint, then, granting the existence of both constrictor and dilator nerves, in direct relation with the sciatic, what would be the result of electrical stimulation? *None, whatever*,—diameter, structure, and peripheral elements of the nerves being equal. Function depending on increased blood-supply and perfect balance between vasodilation and con-

striction being the fundamental requirement of normal activity, the conductivity of both nerves must be equal; hence, this position may be taken as a working basis. But quite another result is to be expected when, as is actually the case, the sciatic is to be considered as a factor of the problem. A large motor nerve *plus* the constrictor *plus* the dilator no longer represents balance as to conductivity, and my analysis must now include, as an element, the fact that the energy distributed to the vaso-dilator nerve will, all else being equal, be as its circumference is to that of the sciatic and the vasoconstrictor combined. When the great size of the sciatic is recalled, it becomes evident that the dilator will at best receive an insignificant proportion of the current. Under these circumstances what experimental results could we expect? Section would obviously cause dilation, since the dilator nerves would be cut, and the tonic contraction of the vessels would also be annulled through section of the constrictor. Electrical stimulation of the peripheral stump of all the nerves, therefore, could have but one result,—constriction,—since the dilators receive practically no current. This agrees perfectly with observed facts. But why the opposite result also observed? This renders it necessary to analyze what evidence there is as to the actual existence of vasoconstrictors in striated muscles.

“With regard to the vasoconstrictor fibers,” says Professor Foster, “*the only evidence* that they exist in muscles is that when the nerve of a muscle is divided the blood-vessels of the muscle widen, somewhat like blood-vessels of the ear after division of the cervical sympathetic. This suggests the presence of vasoconstrictor fibers carrying the kind of influence which we called tonic, leading to an habitual moderate constriction; it cannot, however, be regarded by itself as conclusive evidence.” We have seen that vascular constriction is unmistakably associated with the sympathetic system: its only source elsewhere. No fibers of the sympathetic are associated with skeletal muscular tissue. In fact, Professor Foster, referring to the latter, says: “The presence of any vasoconstrictor fibers at all has not at present been satisfactorily established. When a muscle contracts there is always an increased flow of blood through the muscle,” thus simultaneously suggesting the pos-

sible absence of vasoconstrictors and indirectly confirming the presence of vasodilators.

The question, therefore, becomes an open one, and, if it is considered from the standpoint of my conception of the process of muscular contraction,—*i.e.*, with the vasodilators as the inciting factor of the oxidation process that underlies muscular activity,—the contradictory phenomenon referred to—*i.e.*, *dilation* under electrical stimulation—may be accounted for, provided, however, vasoconstrictor nerves are eliminated from the function involved.

Foster states that “this vasodilator action is almost sure to be manifested when the nerve is divided and the peripheral stump stimulated *some days* after division, by which time commencing degeneration has begun to interfere with the irritability of the nerve. For example, if the sciatic be divided, and some days afterward, by which time the flushing and increased temperature of the foot following upon the section has wholly or largely passed away, the peripheral stump be stimulated with an interrupted current, a renewed flushing and rise of temperature is the result.” As I interpret this result, the stimulation means vasodilation. But I have stated that the sciatic, owing to its greater size, would practically alone transmit the energy, leaving the vasodilator uninfluenced, and, if we transfer to the sciatic the constrictor function, the effect should be the opposite of that observed. That a better conductor than the vasodilator is present is shown by the sentence “the constrictor fibers also appear to be more readily affected by a tetanizing current than the dilator fibers.” The sciatic itself being looked upon by me as the vasoconstrictor, we can, therefore, connect the remark with this nerve. Bearing this fact in mind, we will now inquire into the comparative behavior of the sciatic as a motor-constrictor nerve with its antagonist, the vasodilator, under the conditions mentioned: *i.e.*, section, followed some days later by stimulation, utilizing quotations from Professor Foster’s text as the basis of my analysis.

Referring to the sciatic and brachial plexus, he says: “The constrictor fibers appear to predominate in these nerves, and hence constriction is the more common result of stimulation.”

Considered as motor constrictors these nerves would respond to stimulation in precisely this manner. "Exposure to a low temperature again seems to depress the constrictors more than the dilators; hence, when the leg is placed in ice-cold water stimulation of the sciatic even when the nerve has been but recently divided, throws the dilator only into action, and produces flushing of the skin with blood." This demonstrates at least an intimate association between motor and constrictor functions. Again, since placing of the limb in ice-cold water abolishes response of the sciatic to stimulation, this nerve must readily succumb functionally to untoward influences—evidently sooner than the vasodilator. This is confirmed by the statement: "The latter" (the vasodilators), "in *contrast* to ordinary motor nerves, retain their irritability after section of the nerve for very many days." Again does the link between the motor and the constrictor element appear, and as they jointly succumb while the dilators retain their irritability, and the loss of function under pathogenic influences begins much sooner than in the latter, we are brought to recognize, first, that motor and constrictor nerve-elements are either pathologically affected in precisely the same manner, or that both functions are attributes of the motor nerve; second, that we have in the histological changes incident upon section of the latter, or the nerves of the brachial plexus, the cause of vascular dilation that ensues upon stimulation, when this experimental procedure is not carried out at once.

And, indeed, the strength of this proposition appears if we examine the histological structure of any nerve-bundle, and particularly such organs as the sciatic. The many elements that enter into their organization suggest immediate morbid alterations on section, especially if my view that the blood-plasma is the vehicle or excipient of the oxidizing substance which maintains all functional processes is warranted. Under these conditions, it is plain that cutting of the nerve should at once initiate degenerations, the morbid process and the resulting loss of functional powers progressing until, "at a certain stage, a stimulus, such as the interrupted current, while it fails to affect the constrictor fibers, readily throws into action the dilator fibers."

But why do the dilator fibers not degenerate likewise? Inasmuch as, quoting Professor Foster's words, "the presence of any vasoconstrictor fibers at all has not at present been satisfactorily established," while "the only evidence of their existence" is that, "when the nerve of a muscle is divided, the blood-vessels of the muscle widen," we must admit, in the face of the foregoing statements, that all the evidence now tends the other way: *i.e.*, to suggest that the sciatic and the brachial-plexus nerves are not only motor, but also vasoconstrictor nerves, and that dilators are autonomous structures—if they exist at all in a muscle.

Referring to the effects of severance of a nerve from the central nervous system, Foster says: "When a nerve—such, for instance, as the sciatic—is divided *in situ*, in the living body, there is, first of all, observed a slight increase of irritability, noticeable especially near the cut end; but after awhile the irritability diminishes and gradually disappears. Both the slight initial increase and the subsequent decrease begin at the cut end and advance centrifugally toward the peripheral terminations. This centrifugal feature of the loss of irritability is often spoken of as the Ritter-Valli law. In the mammal it may be two or three *days*; in a frog, as many, or even more *weeks*, before irritability has disappeared from the nerve-trunk. It is maintained in the *small* (and especially in the intramuscular) branches for still longer periods." This obviously suggests that *the size* of a nerve, all else being equal, is a governing factor in the degenerative process due to nerve-section, precisely as indicated when the relative effects of the electric current were referred to.

Still, such a governing principle would necessitate that a large nerve be structurally similar to a small one, qualitatively and quantitatively, to warrant our accepting it as the basis of a final conclusion. Such is not the case, however, as is well known. While the various structures that enter into their formation are specific to nervous organs, they are not evenly distributed. This is illustrated in the case of vasomotor nerves. Though both constrictors and dilators are medullated, the former lose their medulla *early* in their course, while the vasodilators preserve theirs until the blood-vessels to which they

are distributed are *almost reached*. We must also remember that this medulla is an extremely complex body. "Being so complex," says Professor Foster, "it is naturally very unstable, and, indeed, in its stability resembles putrid matter. Hence, probably, the reason why the medulla changes so rapidly and so profoundly after the death of the nerve." Viewed from my standpoint, this suggests that, inasmuch as the vasodilator fibers preserve their medulla until the vessels to which they are distributed are nearly reached, they should degenerate *before* the constrictors, which lose theirs early in their course. And such would be the case *did any such nerves exist* in the sciatic or brachial-plexus nerves or any nerve of the skeletal muscular system. Indeed, were there any, their functional activity would outlive that of the vasodilators, which is not the case. If this fact is now considered in association with the other features of this analysis, it seems to me to suggest that *the voluntary muscular system is not supplied with separate vasoconstrictor nerves*, but that *the functions of the motor nerves distributed to these muscles include that of vasoconstriction*.

Further evidence that this conclusion must represent the actual state of things is afforded by the manner in which it simplifies—provided, of course, previous conclusions are likewise admissible—the whole process which underlies voluntary muscular activity, without in any way contradicting the data sustained by experimental evidence. Indeed, vasoconstrictors have never been found; an element of confusion is thus removed which will probably enable us to ascertain the actual effects of nerve-impulse on the voluntary muscular fibers and their purpose. As to the vasodilators, another element of confusion is removed through the fact that we now know from data recorded in these pages that they need extend no farther than the ultimate vascular subdivision, the walls of which contain muscular elements: *i.e.*, the *arterioles*. The fact that the oxidizing substance of the blood-plasma reaches the muscular elements themselves and can there exercise its life-sustaining power and suddenly awaken activity also simplifies a very perplexing question. The capillaries which entwine the muscle-fibers simply allow their plasma to ooze out through their stomata, or endothelial-plate interstices, and thus to reach the

contractile substance through the latter's own investing membrane. Increase of plasma means increase of work: *i.e.*, muscular contraction. Waste-materials are as rapidly returned through efferent capillaries to the venules, thus leaving the field clear for continuous function.

While I have greatly simplified the processes mentioned, I have complicated another, since it now becomes necessary to account for the functions implied by "voluntary," "motor," and "constrictor," all through the operation of one set of nerves. And yet I am now in perfect accord with the anatomical side of the question, since there is no evidence that constrictor nerves exist. The *only* nerve distributed to a voluntary or striped muscle proper, the motor nerve, enters its sheath, breaks into numerous subdivisions, and thus sends one filament—occasionally two—to each muscular fiber. On the surface of the latter, near the middle, an important terminal arrangement prevails: *i.e.*, each nerve-fiber develops its "motor end-plate." Its white matter of Schwann ceases and its outer covering becomes continuous with that of the muscle, so that its *axis-cylinder alone* penetrates to the muscular fiber. Here it subdivides into numerous root-like processes, forming a hillock, or motor end-plate, supported by a layer of granular substance which contains a number of large nuclei. It is this end-plate that the impulse first strikes when it reaches the muscular fiber, and it travels from the center of the latter to the two ends. All the elements of the muscle are so disposed as to receive the impulse simultaneously.

Before analyzing the mechanical result of this impulse or going further into the vasodilator question, a brief allusion to the histology of the arterioles of voluntary muscle must be made. The internal coat is composed, as elsewhere, of endothelial cells; when the middle coat is cut transversely, however, it presents a peculiar conformation: *its outline is festooned*. Ranvier⁵ divides the middle coat into two layers: an internal elastic lamina and a muscular layer. In his description of these structures he says: "The internal elastic lamina, as is the case with all parts formed of elastic substance, possesses

⁵ Ranvier, quoted by H. Berdal, "Histologie Normale," 1894. .

but little elasticity, and, when it is compressed by the muscular layer encircling it, it happens that the lowest limit of its elasticity is surpassed and that, in order to accommodate itself to the restricted space reserved for it, it forms folds. It is for this reason that a transverse section causes it to appear as if festooned, while longitudinal sections of these small arteries, owing to folds formed during muscular retraction, give the appearance of longitudinal striae." From my point of view this is subject to another interpretation. Indeed, this festooning in *longitudinal* folds,—observed to a limited extent in all small arteries,—coupled with the effects of muscular retraction, seems to me to point distinctly to the mechanical process through which efficient changes in the caliber of the arterioles are insured.

The impulse, we have seen, travels from the end-plate toward the extremities of the muscular fiber and *the muscle contracts*, according to my view, *as the result of dilation of the arterioles*. While the sudden onset of oxidizing plasma, by suddenly increasing the production of chemical energy, which in turn is converted into contractile energy, accounts for the latter, it does not account for the "voluntary" element of the process, nor for the wonderful precision which characterizes muscular movements—those of the fingers, for instance. Indeed, myosinogen *plus* the oxidizing substance must be considered—if my doctrine prevails—as the only source of work, but not as the intermediary through which the volition (conscious or unconscious) implied by the word "voluntary," and the functional control that this implicates, is obeyed. In other words, it constitutes what in the locomotive is represented by the combination of fire, water, and steam, but it does *not* represent the throttle-valve, which is subject to the will of the engineer. His "voluntary" act, transmitted through the lever, regulates the quantity of steam admitted into the cylinder—in which heat is transformed into work. In the muscle each "fine, transparent, membranous tube" is a cylinder, but one in which the conversion of energy into work is the result of a local process in which myosinogen *plus* the oxidizing substance are the *sources* of energy. The throttle-valve is obviously the arteriole, but so located as to admit—as

regards contraction—a surplus, not of fuel, but of the active element which underlies the effects of “draught” in the engine: *i.e.*, oxygen, that carried by the oxidizing substance. The fuel—myosinogen—is always present in our muscles—when they are normal, and the activity of the combustion is regulated there, as elsewhere in Nature, by the quantity of oxygen admitted. Yet, how is the conscious or unconscious control implied by the word “voluntary” carried out?

The muscular arteriole during complete muscular retraction is only just sufficiently patent to allow the passage of enough blood-plasma containing the oxidizing substance to sustain the nutrition of the muscular tissues, and other processes through which their functional efficiency is insured. But the fact must not be overlooked, as emphasized by Foster, that the relaxation is an essential part of the whole act; indeed, no less important than the shortening itself. Again, a completely retracted muscle is not a relaxed muscle; it is precisely in the opposite state,—*i.e.*, in a condition of tension between its insertions,—and if either one of the latter be cut the muscle recedes toward the other. This feature is well exemplified after amputations. The biceps can contract unimpeded, for example, three times the extent that its skeletal attachments will normally allow; fractures of the olecranon or of the patella are familiar examples, notwithstanding the fact that the muscles thus liberated at one end are held partly retracted by the surrounding structures. Indeed, a normal muscle can aptly be compared to a piece of rubber stretched between two fixed points, and contraction really represents a relaxation of the stress. But there are variations in the resistance to which this stress is submitted, and it is here that the identity of the controlling concept appears as an independent factor, while that of the motor mechanism also emphasizes itself by phenomena that cannot logically be considered as elements of the process through which the “voluntary” impulse is transmitted, nor of the transmitting organs, the motor nerves.

If the arm is flexed, say, at an angle of 90 degrees, it can be held in this position without fatigue for some time. But if a sufficiently heavy weight be placed in the hand, the arm remaining in precisely the same position, marked evidences of

strain appear: the face becomes flushed, the superficial veins enlarge, more or less sweating occurs, etc.: *i.e.*, all the familiar signs associated with continued effort assert themselves. Resistance evidently underlies the whole process, and, as "resistance" always implicates at least two contending forces, we are led to divide the process itself into two parts: *i.e.*, the weight which tends to force the hand down and the muscular effort exerted to hold it up. But if we analyze the muscular effort, it soon becomes apparent that it is itself susceptible to a clearly defined subdivision. Indeed, notwithstanding the weight, the arm *remains fixed* in one position; and the entire organism shows the effects of strain; muscles other than those of the arm contribute work, the entire circulatory system (including the heart, judging from its overaction) enter into a phase of unusual activity, etc.,—all laboring to the one end, *viz.*: to mechanically satisfy, regardless of the aggregate of energy converted into work, the needs of the voluntary act *physically impressed upon the muscle* and transmitted to it from the brain through the motor nerve. We thus have, on the one side, a form of volitional energy through which the muscle is *fixed* in the one position; and, on the other, an oxidation process, through which muscular work is carried out, sustained, and intensified to the highest possible degree compatible with the body's strength.

That two distinct processes are present may be shown in several ways. Professor Foster, referring to the "*impulse-wave*," states, for example: "It is *followed* by an explosive decomposition of material, leading to a discharge of carbonic acid, etc." Not only does the active reaction occur *after* the dispersion of the impulse, but Helmholtz ascertained that quite a perceptible and computable period of time elapsed between the two phenomena. By means of the Marey myograph this "latent period" was found to occupy one-sixtieth of a second, while the maximum contraction is only reached at the end of about one-sixth of a second^o in an average muscle. A radical difference is also evident in the relative ability of the two kinds of energy—volitional and motor—to undergo fluct-

^o M. Duval: *Loc. cit.*, p. 151.

uations in what, for the sake of convenience, we may call "intensity." The impulse-wave simply *sets* the muscle-elements to a given vibratory rhythm, and they retain this, whatever be the intensity of the exertion required. The oxidation process, on the contrary, contributes whatever degree of mechanical energy is necessary to fulfill the needs, not only of the movement, but also of any additional work any increase of resistance may demand. Thus, the impulse-wave may fix the muscles of the flexed arm in a given position, but any fluctuation in the power required to support different weights is at the expense of the motor mechanism. This may be aptly compared to the manner in which a note on a violin is made loud or soft. The power with which the string is pressed upon with the moving bow modifies the intensity of the sound; but the note remains the same. This means that its *pitch* does not vary, and if, for example, the lower C is given, we will know that the *sound-wave* of that note represents 261 vibrations per second. So may the *impulse-wave* transmitted by the brain through a "motor" nerve be represented by a fixed number of vibrations. Retraction, the muscle being then most tense, is therefore characterized by the greatest number of vibrations. On receiving the impulse the muscle adjusts itself, whether by contraction or retraction, to precisely the extent which the number of vibrations transmitted will allow, and remains *fired* in the state of contractility assumed until the impulse-wave itself is modified. The *power* or *intensity* of sound and the variations in the work this implies are fully typified by the motor process, through the enhanced circulatory activity and a corresponding increase in the *rapidity with which the oxidizing substance (adrenoxidase) is brought into contact with the myosinogen in the muscles*. It is simply a question here of more fuel and more draught.

Obviously, the rhythm transmitted to a voluntary muscle is simultaneously communicated to the muscular walls of its vessels by the same impulse. The lumen of each vessel—veins as well as arteries, since the former also possess a muscular coat, but much less important structurally and therefore less active—varying synchronously with the muscle to which it is distributed, the flow of blood through it is exactly adjusted

to the needs of any degree of muscular contractility the voluntary (conscious or unconscious) movement requires. In other words, *the arteries, and to a certain extent the veins, become constricted or dilated proportionately as the muscle is contracted or retracted*, and the activity of the motor mechanism is thus concurrently adjusted to the functional requirements of the moment.

If this conception is not erroneous, the general process it represents certainly constitutes a marvelously simple way of accomplishing many of the most important functions of the organism, since those ascribed to both vasoconstrictor and vasodilator nerves are thus performed without, indeed, leaving a single reason for the presence of *either of these nerves as independent entities*.

This normally suggests the question: Do vasodilators actually exist in muscular vessels? That there are vasodilators in certain organs: the submaxillary and other salivary glands, the tongue, the penis, etc., is thought to have been experimentally demonstrated; but their existence in the muscular vessels has not been shown, the evidence adduced, as was the case with the constrictors, being purely inferential. We have seen that section of the sciatic, followed by stimulation after some time had elapsed, caused dilation of the vessels of the extremities, while earlier it had caused constriction. Close analysis also showed that actual dilation of the arteries could be ascribed only to an *active* dilator action. The only remaining feature that requires elucidation, therefore, is the manner in which this is carried out. Does the above-described process account for these contradictory phenomena as well as would vasodilator nerves? That the elastic lamina of the vessel can fulfill precisely the same function as the latter seems evident.

The impulse-wave being accepted as the governing factor, each point of the muscular coat is caused to recede or approach from the axial line of the vessel just sufficiently to bring the caliber of that vessel to the required limits. Hence the presence of the muscular coat *over* the elastic lamina. The cause and purposes of the latter's longitudinal corrugations now become apparent: while perfectly elastic, it is somewhat larger in diameter than the muscular layer, and, lying, as it does,

within the latter, it forms the folds or "festooning" described by Ranvier. Viewed from my standpoint, however, these longitudinal folds play a very important part in the whole mechanical process described, since it is upon variations of their outline that the adjustment of the lumen of the vessel mainly depends. Mere dilation of a circular vessel, of course, involves an increase in the diameter of the stream passing through it; but, if numerous folds that project into that stream are simultaneously withdrawn by being leveled out, it is evident that the free space within the vessel will be vastly increased, and that a much greater range between dilation and contraction will thus be available.

That such is the process through which a slight variation of the peripheral pressure exerted by the muscular layer will cause a relatively larger variation of the amount of blood to pass through the vessel seems very probable, since it satisfies all mechanical needs. As long as the characteristic impulse-wave of a fixed degree of muscular contraction persists, the vessels are simultaneously adjusted to the needs of this particular degree of contraction and allow just the necessary amount of blood—*i.e.*, oxidizing plasma or adrenoxidase—to pass.

Returning now to the contradictory results of stimulation of the sciatic after section of that nerve, an important feature must be referred to, which, if considered before, would have but introduced confusion in the inquiry: *i.e.*, the fact that stimulation of this nerve immediately after section may either be followed by dilation or constriction. Laryngologists are quite familiar with the fact that one strength of current will cause adduction of the vocal bands,—*i.e.*, of their muscles,—while another strength will cause the opposite condition—abduction,—when the recurrent laryngeal nerve is cut and stimulated. That the same controlling factor must prevail in the case of the sciatic is very probable, if, as we have suggested, the rhythm of the impulse-wave determines the degree of muscular contraction. The certainty with which dilation is produced when the nerve is stimulated "some days after division" is a phenomenon of another sort. The electric current does not, like a normal nerve-impulse, select a physiological path; it simply utilizes the channels that offer the least resistance.

A diseased sciatic means impairment not only of its conductivity, but also of that of its subdivisions. The current may or may not, under these conditions, continue to follow the nerve stimulated after the segment buried in the tissues is reached; selecting the best conductors, it will, if it follow the course of the vessels, mainly stimulate the layer offering the least resistance: *i.e.*, the thickest and softest, as regards inherent proportion of fluids. As this characterizes the elastic layer, it cannot but receive the brunt of the stimulus. We are no longer dealing with muscular vibrations, but with a corrugated elastic tube the normal tendency of which is to expand, level its folds, and *increase* its lumen. The current, by inducing crethism, encourages this, and produces, by increasing the caliber of the vessels, "flushing and increased temperature of the foot." Indeed, electricity is a poor substitute for the physiological impulse-wave and sometimes a misleading one.

We can fully agree with Professor Foster, therefore, when he says: "There is no adequate evidence that these vasodilator fibers serve as channels for tonic dilating impulses or influences" but because, in the light of our views, *both functions are fulfilled by the nerves which govern function.*

Indeed, it is when we attempt to explain the process through which a motor nerve carries on its functions, and realize that it is because an organ in action is traversed by more arterial blood than an organ in repose that the need of a nerve to dilate the arteries which admit the excess of blood, and of another nerve to restore them to their normal caliber that the strength of this conclusion asserts itself. As will be shown in the second volume (p. 1185), a "motor nerve" is in reality a dilator nerve, while the resumption of the arterial caliber after function is insured by sympathetic vasoconstrictor filaments. In other words:—

1. *The arterioles of voluntary muscles are supplied with motor-filaments which cause them to dilate when contraction is to occur, and with sympathetic filaments which cause them to resume their normal caliber when the contraction is to cease.*

Source of muscular energy: *an oxidation process in the muscular contractile elements the chemical energy of which, after conversion into mechanical energy, supplies the muscle*

during any stage of contraction or retraction with the power-to-do-work required to sustain either of these functions.

This oxidation process is subject to fluctuations of activity, and occurs as the result of a reaction between two physiological compounds: first, myosinogen,—i.e., blood-plasma containing various carbohydrates and immanent in the muscle-fiber,—as a potential; second, an oxidizing substance (adrenoxidase) also contained in the blood-plasma, but in that of the arteries, as reagent.

2. As to mechanical process: *variations in the caliber of the muscular vessels give rise to corresponding variations in the proportion of oxidizing substance (adrenoxidase) admitted to the myosinogen in the muscular fiber and to correspondingly marked fluctuations in the activity of the oxidation process.*

The myosinogen is stored in the contractile disks while the adrenoxidase-laden plasma fills the interstitial disks, and an opening between the two probably exists through which this plasma is forced when the impulse-wave adjusts the muscle to the required contraction, the quantity of energy produced being thus simultaneously adjusted to the needs of that contraction.

THE ADRENOXIDASE AND THE MOTOR NERVES IN THEIR RELATION TO GLANDULAR SECRETION.

In the foregoing pages I have sought to elucidate the manner in which the voluntary muscular system could be functionally related with vasomotor functions. I have suggested, moreover, that the sympathetic system, which has been credited by different observers with secretory, inhibitory, motor, and vasoconstrictor functions, plays an important rôle in voluntary muscles in conjunction with motor nerves. Acting jointly, they were shown to adjust these organs to a specific degree of activity, and simultaneously to adapt the lumen of its vessels to the needs of this functional activity in order to 'admit precisely the amount of blood—i.e., of oxidizing serum—required. This principle may be said to prevail in all organs, the many varied functions attributed to the sympathetic notwithstanding. Obviously, each organ contains, as inherent source of energy, either endogenous products with which the oxidizing substance combines, or cellular structures whose metabolism is sustained

by the oxidizing substance. This is a question, however, that will be taken up as each organ is studied.

The classic division into two independent systems, cerebro-spinal and sympathetic, may be regarded as conclusively established in its general lines. Their mutual relations are still obscure, however, though it may be said that at all times some connection or other with the cerebro-spinal axis, whether it be associated with borrowed or direct impulses, has been attributed to the sympathetic nerve-paths. This is well illustrated in a comprehensive paper, in which the functions of the sympathetic system are ably reviewed, by B. Onuf (Onufrowicz) and Joseph Collins,⁷ who refer to tonic vascular contraction as follows: "It has been shown that many nerves of the sympathetic system are under the tonic influence of spinal or cerebral centers. Section of the cervical sympathetic nerve is followed by dilation of the blood-vessels of the head; section of the abdominal sympathetic by dilation of the blood-vessels of the hind-paws; section of both splanchnics by the same phenomena in the stomach and the intestine. Severance of the nerves connecting the submaxillary ganglion with its encephalic center gave rise to an increasing continuous secretion of the submaxillary glands, proving the regulatory influence of the cerebro-spinal system upon the submaxillary ganglion (Claude Bernard)."

If we now recall the limitations of the adrenal system described in the last chapter,—*i.e.*, the triad: thyroid, anterior pituitary, and adrenals,—and particularly the connection between the two latter organs through the cord, the sympathetic ganglia and the splanchnic nerves, the following remarks of the same authors are especially interesting: "Regarding the tonic influence of ganglia of the sympathetic itself, the views still differ. . . . We know, however, that the heart removed from the body still continues to beat, and that the bladder deprived of motor nerves leading to it continues to perform its functions." They also refer to the observations of Contejean, "according to which the secretion of gastric juice continues after the stomach has been deprived of all its nerve-connections." The reason for this is now clear. Inasmuch

⁷ B. Onuf and Joseph Collins: *Archives of Neurology and Psychology*, vol. III, Nos. 1 and 2, 1900.

as the motor nerves merely incite motor or secretory activity by vasodilator filaments, severance of the nerve-supply of an organ does not disturb its vessels, and, as the agency that supplies it with working energy reaches its tissues through the blood, it is plain that its functional activity should continue, even when its motor nerves are severed.

As regards the tonic contraction of vessels ascribed to the sympathetic vascular fibers, it is merely the result of the *continuous*, though passive, activity in which all muscular tissues are held by the oxidation process, which continues as long as blood flows in physiological channels. This includes the circulation through the intermediary of the vasa vasorum, of oxidizing plasma into the contractile elements of the muscular fibers of the vascular walls, and its return to the blood-stream *per se* charged with products of combustion. As previously stated, these do not only represent the products of hydrocarbon combustion, the specific source of muscular energy, but also those resulting from metabolism of the cellular elements *per se*. In other words, a relatively small amount of oxidizing plasma is incessantly penetrating to the myosinogen and causing the development of just sufficient energy to insure nutrition of the tissues and to keep them in that *potential* state in which, though not doing active work, they are ever ready to actively respond to summonses: *i.e.*, to "motor-nerve" impulses. A skeletal muscle, held by its two insertions, is not free to contract in obedience to what energy the continuous oxidation process generates, and, not being at once converted into work, this energy is dissipated as heat. But not so with the vascular walls; having only the centrifugal resiliency of their inner coat to contend with, they at once convert the chemical energy generated by the reaction in their contractile elements into work which manifests itself as "tonic" contraction.

If my view is based on a solid foundation, I must, however, be able to show that all the nervous structures comprised under the name of "sympathetic" are only capable of causing constriction of the vessels (the arterioles) to which they are distributed. It is well known, for example, that when the cervical sympathetic chain is severed, the phenomenon produced is, as stated, dilation of the vessels of the ear, which can

be overcome by stimulation of the cephalic end of the cut nerve. I must also account for the phenomena witnessed at least as well as they are by the older doctrine. In this experiment it is plain that the dilation of the vessels ensues owing to the *loss* of their constrictor nerve-impulse. The fact that the local temperature rises shows that the oxidation process is enhanced owing to the admission of an excess of blood into the tissues. On the electric current being applied the nerve-impulse is replaced, the recontracted vessel overcomes the exaggerated blood-flow, and normal conditions are restored. This reduction of the sympathetic system to the rank of a vasoconstrictor system seems a radical departure from the many different rôles that have been ascribed to it—an obvious proof of the existing obscurity concerning its true function—but it is, nevertheless, substantiated by facts. Thus, in the article previously referred to, Onuf and Joseph Collins,^{*} after a very brief reference to the many observers who have given the sympathetic system especial attention, including Pourfour du Petit, Claude Bernard, Schiff, Vulpian, Dastre and Morat, Luchsinger, Heidenhain, Gaskell, and Langley, they outline its functions as follows: "It may safely be concluded that it has, to a great extent, a controlling influence over the secretion of most of the glands, the lacrymal, the salivary, the sweat-glands, the glands of the stomach and intestines, the liver, the kidney, etc.; that it presides over the circulation by regulating the caliber of the blood-vessels and the action of the heart; that it influences respiration; and finally that all the involuntary muscles, those of the digestive apparatus, of the genito-urinary system, of the hair-follicles (pilomotor nerves) are under its control." And yet all these apparently dissimilar functions can, when traced to their original cause, be ascribed to variations in the caliber of the arterioles, which admit, as is well known, arterial blood into all tissues. The "controlling" influence on glandular organs of sympathetic fibers is readily explained when their rôle is restricted to that of arteriole vasoconstriction, since as such they can increase or decrease the volume of blood admitted into these organs. This applies as well to their connection with

^{*} B. Onuf and Joseph Collins: *Archives of Neurology and Psychopathology*, Nos. 1 and 2, vol. III, 1900.

the muscles, the digestive and genito-urinary systems, etc., in fact to all organs. Even the so-called "inhibitory" functions ascribed to the sympathetic by some physiologists can be accounted for by its constrictor action on the arterioles, since excessive constriction, such as that produced experimentally by the electric current, is capable of reducing the caliber of these small vessels sufficiently to arrest, *i.e.*, inhibit, function.

We shall successively review each of the functions referred to, beginning with those that present the simplest mechanism,—*i.e.*, the lacrymal, salivary, sudoriferous, and mammary glands.

LACRYMAL GLANDS.—Present knowledge as to the innervation of glands in general, judging from a perusal of its literature, is well exemplified by Matthews, who, after a careful study of the question, says: "Whether secretory nerves exist or whether secretion is ever a function of the gland-cell must be considered at present an open question."

To elucidate the connection between the sympathetic and the lacrymal gland Onuf and Collins removed one stellate^{*} ganglion from each of three cats, and reviewed their results as follows: "In one of the cats (three and a half months old) an injection of 1 centigramme of pilocarpine, given three weeks after the operation, produced lacrymal secretion of the eye of the normal side, while the eye of the operated side remained dry. In the second cat (about two months old) 5 milligrammes of pilocarpine were injected one month after the removal of the left stellate ganglion. In this case the result was altogether different. Both eyes wept, but the eye of the operated side more profusely than the other. About an hour after the injection there was still considerable lacrymal secretion from the eye of the operated side, while the other eye was dry. In the third cat (about six weeks old) an instillation of a 2-per-cent. solution of pilocarpine was made in both eyes, four and one-half months after the operation. The effect was an equal amount of lacrymal secretion in both eyes." The authors then close the subject with the following remarks: "These results are rather contradictory, and further experimentation must be made to harmonize them and to allow of a correct interpreta-

^{*} In the cat this ganglion constitutes what in man would be the three cervical and the first thoracic ganglia coalesced.

tion. It must be taken into consideration, of course, that the age of the animals varied, as did also the period (after the operation) at which the pilocarpine was administered. The manner of administration of the poison was different also."

Viewed from my standpoint, these experiments do not appear contradictory; indeed, they may enable us to ascertain the identity of the nervous structures involved and the manner in which the functions of the gland are carried out. Obviously, removal of the stellate ganglion on the one side severed the sympathetic filaments supplied to the glandular vessels. As is shown in the second volume (p. 1185), sympathetic nerves are distributed to the arterioles only and, moreover, they increase the *propulsive* action of these small vessels, owing to the fact that the muscular layer of the latter is *disposed spirally around them*. If we now take into account the fact that pilocarpine produces lacrymation by causing paresis of the arterioles and dilation of these vessels (see page 1381) the results obtained by Onuf and Collins can all be accounted for—provided other physiological facts are not overlooked. One of these is that a vessel recovers its normal caliber about ten days after its vasomotor nerves are severed—a procedure which, of course, had allowed the vessels to relax. Again, the stellate ganglion might not alone have supplied vasomotor filaments to the cervical cord. On the whole, there is good ground for the belief that the innervation of the lacrymal gland in Onuf and Collins's animals had recovered more or less their influence on the arterioles of these organs. Hence the fact that in the first cat one eye remained dry; its sympathetic nerves having not as yet recovered their influence, the pilocarpine did not cause dilation of the arterioles supplied to its lacrymal gland, while, that on the normal side being rendered hyperemic by the paresis of its vessels, lacrymation occurred. In the second animal the vascular nerves on the operated side had resumed their functions but failed to recover from the effects of the drug as soon as the normal eye. In the third cat the nerves had completely resumed the functional activity; or collateral nerves, including perhaps some derived from the cervical region of the spinal cord, had taken up functions of the severed nerves.

This has served to illustrate not only how the functions of

an organ depend upon the blood circulating through it, but also that its motor—secretory in this instance—nerves are vaso-motor.

The foregoing facts seem to suggest that the sympathetic is the secretory nerve of the lacrymal gland. Indeed, this is in accord with the prevailing teachings: while, for example, the secretory activity of the submaxillary gland is credited to the chorda tympani, a branch of the facial, and that of the gastric mucous membrane to the vagus, although both these organs are supplied with sympathetic nerves, the latter are granted secretory functions in various organs. There is considerable evidence to show, however, that in the lacrymal gland as elsewhere, the sympathetic subserves the same functions that it does in all organs, viz., those of insuring the propulsive activity of the arterioles, *thus simulating secretory activity*, and of causing them to resume their normal caliber after dilation by the secretory or motor nerve which incited function.

The erroneous belief that the sympathetic is the true secretory nerve of the lacrymal gland is based mainly on the following data: Denitschenko,¹⁰ Wolferz, Bechterew and Mislawski¹¹ observed an increase of lacrymal secretion on stimulating this nerve. Herzenstein¹² failed to observe this effect on stimulating either the cervical sympathetic or the fibers proximal to the gland. Reich,¹³ on exciting the latter, observed tears occasionally; Arloing¹⁴ never in the goat and ox (the other investigators had used cats and dogs); neither did Campos¹⁵ in the monkey. The weight of testimony tends toward the affirmative, therefore, but the first observers named state that the secretion obtained differs physically from the normal and that it is cloudy. This assimilates the product obtained from the submaxillary gland by exciting the same nerve, *i.e.*, an artificial secretion.

But another nerve also produced lacrymation when stimulated: the facial. Goldzieher,¹⁶ having noted that paralysis of

¹⁰ Denitschenko: *Pflüger's Archiv f. Physiol.*, Bd. vi, S. 191, 1872.

¹¹ Bechterew and Mislawski: *Neurolog. Centralbl.*, Bd. x, S. 481, 1891.

¹² Herzenstein: Cited by Campos: *Archives d'Ophthalmologie*, Sept., 1897.

¹³ Reich: *Ibid.*

¹⁴ Arloing: *Ibid.*

¹⁵ Campos: *Ibid.*

¹⁶ Goldzieher: *Ibid.*

the facial arrested lacrymation, concluded that it was the gland's secretory nerve. Tribondeau¹⁷ reached the same conclusion after cutting this nerve. While the corresponding eye showed but slight moisture, that on the unoperated side remained normal. Laffay,¹⁸ after dividing the facial, observed that the eye of the corresponding side remained dry on irritation of the conjunctiva, while irritation of eye on the normal side caused profuse lacrymation. Tepliachine¹⁹ reached the same conclusion, and contended that both in animals and in man the facial branch reached the gland by way of the superior maxillary. Jendrassik²⁰ traced facial fibers from the geniculate ganglion to the sphenopalatine, by way of the large petrosal and vidian nerves, and thence, by way of the orbital branch of the superior maxillary nerve, to the gland. Campos,²¹ to eliminate the possibility of error which the absence of communication between this orbital branch and the lacrymal nerve, observed in certain animals, entailed, experimented upon monkeys. He obtained copious lacrymation by stimulating the lacrymal filament of the orbital branch; on ceasing excitation and drying the eye, no moisture appeared; on resuming it the tears flowed in abundance. Koster²² also caused lacrymation in cats, dogs, and monkey by stimulating facial fibers, after tracing them by exclusion to the geniculate ganglion. It thus seems evident that the facial is the *true* secretory nerve of the lacrymal gland. On the whole, it seems apparent that:—

1. *Overactivity of the lacrymal glands is produced by the circulation through their cellular elements of an increased volume of blood, i.e., of adrenoxidase-laden plasma.*

2. *The increased blood-supply is due to dilation of the glandular arterioles by vasodilator terminals of the facial nerve.*

3. *When lacrymation is to cease, the sympathetic vasomotor filaments also distributed to the arterioles cause them to resume their normal caliber.*

The mechanism of vasodilation will be described presently (p. 274).

¹⁷ Tribondeau: Jour. de méd. de Bordeaux, No. 44, p. 506, 1895.

¹⁸ Laffay: Cited by Campos: *Loc. cit.*

¹⁹ Tepliachine: *Ibid.*

²⁰ Jendrassik: *Ibid.*

²¹ Campos: *Loc. cit.*

²² Koster: Neurol. Centralbl., Nov. 15, 1900.

THE SALIVARY GLANDS.—When the influence of increased blood-supply on functional activity was reviewed, we saw that when the chorda tympani was stimulated after section, the submaxillary gland assumed marked activity; its vessels became greatly enlarged, and its main trunk, which gave passage to blackish blood before the experiment, remained as red as arterial blood as long as the chorda tympani was stimulated. Evidently this nerve is the intermediary of the gland's functions, and Professor Foster is inclined to exclude even the sympathetic as an efferent nerve and to assign all the attributes of such a nerve to the chorda tympani. Some of its fibers, in fact, are, according to this physiologist, "vasodilator fibers acting on the blood-vessels only." As this nerve is generally accepted as the secretory nerve of the submaxillary we have only to point to it as recognized proof of the fact that, as we have pointed out in the case of the lacrymal gland, it is to a nerve which causes dilation—of the arterioles here as before—and admits therefore an excess of blood, *i.e.*, of oxidizing substance into the cellular elements of the gland, that the onset of function, salivation here, is due.

Still, it is difficult to admit with Foster that the many sympathetic fibers along the branches of the facial and lingual that penetrate the organ should hold no place in the active process, since their exclusion as efferent nerves simultaneously eliminates them from the latter. If their influence on the parotid gland can be taken as a standard, however, whatever part they play is certainly not that of secretory nerves, since they compare in no way with the chorda tympani when stimulated. Thus, Onuf and Collins state that "when the parotid gland is thrown into an intense activity by the cerebral secretory nerve so that it secretes from twelve to thirteen cubic centimeters of saliva, the secretion scarcely differs in its microscopical appearance from that of the gland in a state of rest. If, on the other hand, it has secreted from two to three cubic centimeters of saliva under the influence of the sympathetic nerve, the character of the cells is changed to such a degree that one thinks he has to deal with a completely new organ." They also refer to the experiments of von Wittich, which showed that "excitation of the cervical sympathetic nerve remained without effect

upon the secretion of the parotid gland, if the facial nerve of the same side had been torn out from the cranial cavity either immediately or some days before." All this suggests that the sympathetic fibers, which are also distributed to the vessels, are as disconnected from the active function as in the lacrymals: a view strongly sustained by the experimental observations of Heidenhain, which showed that the secretion obtained by excitation of the sympathetic nerve (in dogs or rabbits) was very scarce. That similar experiments in the submaxillary gland have given corresponding results is well known. But the sympathetic cannot be regarded as a secretory nerve on this account since the secretion is merely the result of a slight excess of blood pumped, as it were, into the gland by the increased propulsive activity which the stimulated fibers provoked in the spiral muscular coat of the arterioles.

If the annexed engraving, taken from Professor Foster's work, is carefully examined, it will also be found to show that the circulation of the organ and the sympathetic fibers are intimately associated. The arteries are terminal subdivisions of the carotid, while the veins are primary channels that ultimately lead to the jugular: features which emphasize their functional importance. Over these are entwined sympathetic fibers from the superior cervical ganglion, which fibers are inclosed in a common sheath with the main sensory nerve present, the vagus: further evidence that they must, in a measure, govern the quantity of blood distributed to the organ. In fact, this association with the vagus, sufficiently intimate "to form what appears to be a single trunk," almost imposes the deduction that the arterial branches of the latter nerve transmit the *afferent* or sensory impulses in the reflex arc upon which the "nervousness" of speakers, actors, etc., depends as to the condition of "dry-mouth," or temporary xerostomia, so frequently observed. Such an inosculation is not due to mere hazard; it strongly suggests that the sympathetic fibers form part of the mechanism through which the intraglandular blood-pressure of the organ is governed.

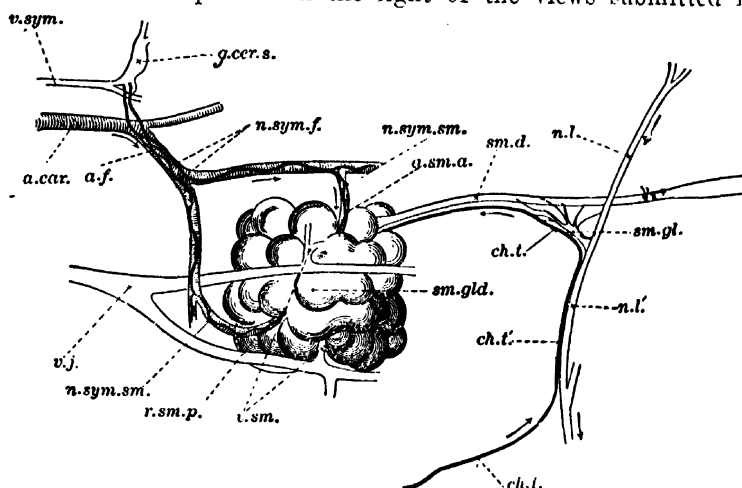
All this shows clearly that the influx of blood regulates the secretory activity of the gland, and that we are dealing with a **vasomotor phenomenon**. This idea would seem to be opposed

by the observation of Ludwig that if, as Howell in the 1905 edition of his text-book states, the "blood-flow be shut off completely from the gland, stimulation of the chorda still gives a secretion for a short time." But if the blood-flow is a secondary factor of the process, why should the secretion cease in "a short time"? The reason for this is plain in the light of my views: the chorda being the secretory, and therefore dilator, nerve of the gland, ligation of all the vessels to the gland did not prevent what blood remained in the glandular vessels to flow in increased quantity into the cellular elements when vasodilation occurred, and to enhance momentarily their secretory activity.

The next question in order is the identity of the process through which a motor or secretory nerve is capable of fulfilling only, as my views suggest, vasomotor functions. We are dealing here not only with a problem of the first importance, but one which physiologists have so far failed to solve. The reason for this is made apparent in the second volume where my own analysis shows that the process is due, strange as it may seem, to vasoconstriction. Indeed, present teachings do not in any way grant constricting powers to the chorda tympani but *active* dilating properties: *i.e.*, it is thought to actually dilate the vessel by relaxing its muscular coat,—the foundation of the belief that vasodilators exist at all.

Is such a mechanical dilation of the arteries or arterioles distributed to the gland possible? The intraglandular supply is mainly composed of capillaries, which, of course, have no muscular coat. The smaller arteries or arterioles end as such soon after entering the organ; as the filaments of the chorda tympani follow the course of these vessels we may surmise that their terminal end-plates are attached to the muscle-fibers of the arterioles; but, to avoid any error on this score, we will consider that they end in the muscular layer of "the small arteries" to which Professor Foster refers. Unless we can ascribe to the nerve-endings themselves the lifting power required to relax the vessels, we must depend on some source of expansile elasticity such as that shown to exist in the vessels distributed to muscles, in the elastic festooned layer described by Ranvier. That the vessels are not mechanically disposed so

as to forcibly dilate the vascular walls hardly needs mention. Nor does an elastic expansile lamina under the muscular layer exist in these vessels, which, besides their muscular coat, are only endowed with an internal endothelial layer and an external adventitious coat. From the standpoint of mechanics, therefore, there is nothing upon which active dilation of the vessels could depend. In the light of the views submitted in



DIAGRAMMATIC REPRESENTATION OF THE SUBMAXILLARY GLAND OF THE DOG, WITH ITS NERVES AND BLOOD-VESSELS.

"The dissection has been on an animal lying on its back, but since all the parts shown in the figure cannot be seen from any one point of view, the figure does not give the exact anatomical relations of the several structures.

"*sm.gld.*, The submaxillary gland, into the duct (*sm.d.*) of which a cannula has been tied. The sublingual gland and duct are now shown. *n.l.*, *n.l.*', The lingual branch of the fifth nerve; the part *n.l.* is going to the tongue. *ch.t.*, *ch.t.*', The chorda tympani. The part *ch.t.*' is proceeding from the facial nerve; at *ch.t.*' it becomes conjoined with the lingual (*n.l.*'), and afterward diverging passes as *ch.t.* to the gland along the duct; the continuation of the nerve in company with the lingual (*n.t.*) is not shown. *sm.gl.*, The submaxillary ganglion, with its several roots. *a.car.*, The carotid artery, two small branches of which (*a.sm.a.* and *r.sm.p.*) pass to the anterior and posterior parts of the gland. *r.sm.*, The anterior and posterior veins from the gland, falling into *v.j.*, the jugular vein. *v.sym.*, The conjoined vagus and sympathetic trunks. *g.cer.s.*, The upper cervical ganglion, two branches of which forming a plexus (*a.f.*) over the facial artery, are distributed (*n.sym.sm.*) along the two glandular arteries to the anterior and posterior portions of the gland.

"The arrows indicate the direction taken by the nervous impulses during reflex stimulation of the gland. They ascend to the brain by the lingual and descend by the chorda tympani." (*Foster.*)

this work, therefore, and particularly since the sympathetic and the chorda tympani are both considered capable only of acting as vasomotor nerves, I find myself obliged, if all my foregoing statements to this effect are sound, to account for the functions of the submaxillary gland with a so-called dilator nerve, the chorda tympani, and a constrictor nerve, the sympathetic.

As to the *vasodilation*, it is easily explained through what I have termed in the second volume (see page 1185) "*stricto-dilation*," which means that the terminal filaments of a motor or secretory nerve, the chorda tympani in the present case, are not connected with the muscular coat of the arterioles themselves, but with the muscular fibers of the vessels which supply the arterioles themselves with blood: their *vasa vasorum*. The manner in which dilation of an artery is brought about under these circumstances suggests itself: *by constricting its vasa-vasorum the muscular layer of an artery receives less blood and relaxes, thus causing the vessel to dilate.*

Hence the effects, as Foster describes them, of stimulation of the chorda tympani: "The small arteries of the gland become very much dilated, and the whole gland becomes flushed." . . . "Before stimulation, the blood trickles out in a thin slow stream of a dark venous color; during stimulation the blood rushes out in a full stream, often with a distinct pulsation."

In keeping with the prevailing views, Foster also speaks of a dual function of the chorda tympani: "When the chorda is stimulated, there pass down the nerve in addition to impulses affecting the blood-supply, impulses affecting directly the protoplasm of the secreting cells, and calling it into action, just as similar impulses call into action the contractility of the substance of a muscular fiber. Indeed, the two things, secreting activity and contracting activity, are very parallel." As will be shown at the end of this chapter, the cellular elements need no nerve impulse to carry on their functions. They do so as marine unicellular organisms are known to do so, by interchanges with the medium in which they bathe—the oxygen-laden water as to unicellular organisms; the oxygen-laden plasma as to tissue cells.

As to *vasoconstriction*, the process through which in the light of my views, the sympathetic fibers restore the dilated arterioles to their normal caliber, it is plainly sustained by the present teachings of physiology. Howell²³ states, for instance, referring to the vasomotor nerves of the gland: "the arrangement of these latter fibers is such that the cerebral nerves contain vasodilator fibers that cause a dilation of the small arteries in the glands and an accelerated blood-flow, while the sympathetic fibers whose stimulation causes a constriction of the small arteries and a diminished blood-flow."

All these facts seem to warrant the following conclusions:—

1. *An exacerbation of activity of the submaxillary gland is produced by the circulation, through their cellular elements, of an increased volume of blood, i.e., of oxidizing substance.*

2. *This increased supply of blood is due to dilation of the glandular arterioles by vasodilator impulses transmitted by the chorda tympani, a branch of the facial nerve.*

3. *When the secretory activity of the gland is to be reduced its blood-supply is correspondingly diminished by constriction of its arterioles under the influence of the sympathetic fibers distributed to these vessels.*

SWEAT GLANDS.—Although text-books now teach that the secretory activity of these organs is due to sympathetic influence, there is no more ground for this view than there is for the acceptance of the sympathetic fibers as the *physiological* secretory nerves in the submaxillary glands. Just as an *artificial secretion* may be obtained from the latter by stimulating their sympathetic supply, however, so can sweat be obtained by causing engorgement of the sweat-glands by provoking local or general vasoconstriction. Indeed, strychnine, which stimulates the vasomotor center, also causes sweating. Conversely, Dupong²⁴ obtained sweating by dividing the cervical sympathetic of the corresponding side of the head—thus causing passive dilation of the arterioles of the gland. We have seen that this is precisely the action on the arterioles of the lacrymal glands, of pilocarpine, whose properties as a diaphoretic are well known.

A careful review of the literature of the subject suggests

²³ Howell: "T. B. of Physiol.," p. 691, 1907.

²⁴ Dupong: Jour. de med. de chir., et pharm., T. xxxvii, 1816.

that just as a secretory cranial nerve, the chorda tympani, normally governs the secretion of the submaxillary gland, so does a cranial secretory nerve govern that of the sweat glands throughout the entire body.

The prevailing view that the sweat-fibers are of sympathetic origin, is based mainly on the observation of Nawrocki²⁵ that the second, third, and fourth anterior spinal roots furnished sweat-fibers which passed up to the skin of the face by way of the cervical sympathetic, because their stimulation caused sweating—a view sustained by Luchsinger²⁶—while excitation of the seventh and ninth cranial gave no result. But no one has shown that the seventh and ninth run to the skin at all. "It is to be borne in mind," writes Langley,²⁷ "that the fibers of the seventh and ninth nerves which run to the fifth *do not*, so far as we know, accompany the branches of the *fifth which run to the skin*, but only those which run to the mucous membrane and glands." Indeed that the *fifth* is the nerve which supplies the sweat glands is suggested by facts submitted below.

This suggests that the functions of the sweat glands are carried on precisely as are those of other glandular structures reviewed. But in the latter, at least, in the lacrymal, parotid, and submaxillary glands, the identity of the secretory nerve was clearly defined. What constitutes the motor nerves of muscles? There is some ground for belief that both the skeletal and sudoriferous muscles are supplied by the fifth pair, an extension of this nerve down the entire spinal cord.

The fact that the motor nerves of the muscles do not reach their destination by way of the sympathetic cord is now generally accepted. Ostroumoff²⁸ found that excitation of the peripheral end of the splanchnic, after section, caused a rise of blood-pressure in the limbs, thus indicating the presence of vasoconstrictors only. This is also sustained by Langley's statement that there is no satisfactory evidence that the sympathetic sends *vasodilator* fibers to skeletal muscles. After saying that the "conclusive form of experiment, as regards vasodilator fibers

²⁵ Nawrocki: Centralbl. f. d. med. Wissensch., Bd. xviii, S. 945, 1880.

²⁶ Luchsinger: Archiv f. d. ges. Physiol., Bd. xxii, S. 126, 1880.

²⁷ Langley: *Loc. cit.*, p. 661.

²⁸ Ostroumoff: Pflüger's Archiv., Bd. xli, S. 219, 1876.

of sympathetic origin is to observe the effects of stimulating the abdominal sympathetic," he refers to the experiments of Gaskell²⁹ who found "a slight decrease of the blood-flow through the muscles," *i.e.*, vasoconstriction, and Heidenhain³⁰ who observed a slight fall of temperature. "Neither found on direct stimulation," says Langley, "evidence of the presence of vasodilator fibers." Bayliss³¹ recently reviewed what evidence had been recorded on the question, and remarks: "It seems to have been almost taken for granted, up to the present time, that the dilators must run in the abdominal sympathetic, but the actual evidence for this is very unsatisfactory." It is clear that the sympathetic, *i.e.*, the vasomotor system, takes no part in the process.

Conversely, there is evidence to show that the skeletal muscles contain vasodilator nerves and that the fifth pair presents attributes which point to it as their motor nerve. Thus Dastre and Morat³² obtained dilator effects by stimulating this nerve in the cranium and also by exciting the Gasserian ganglion, while Laffont³³ caused flushing by stimulating the fifth nerve after the sympathetic fibers anastomosing with it had been allowed to degenerate. Gaskell³⁴ also observed that the branch of the fifth distributed to the mylo-hyoid contained vasodilators. Such effects cannot be attributed to excessive vasoconstriction when a cranial nerve is the source of dilation, since the only connection of the latter with the arteries is—in the light of my views, with the vasa-vasorum of those arteries. They cause dilation or nothing. Moreover, the manner in which its influence on the muscle manifests itself points to a pure motor action. Thus the mylo-hyoid takes part in deglutition, doubtless by transmitting efferent impulses. Starling³⁵ for instance, says: "The *efferent* impulses from the center pass by the hypoglossal nerve to the muscles of the tongue, by the fifth to the

²⁹ Gaskell: *Jour. of Anat. and Physiol.*, vol. xi, p. 360, 1877.

³⁰ Heidenhain: Heidenhain, Alexander u. Gottstein, *Archiv f. d. ges. Physiol.*, Bd. xvi, S. 1, 1878.

³¹ Bayliss: *Jour. of Physiol.*, vol. xxvi, p. 173, 1901.

³² Dastre and Morat: "Recherches sur le Syst. Nerv.," 1884.

³³ Laffont: Cited by Vulpien: *C. R. de l'Acad. d. Sci.*, T. II, p. 381, 1885.

³⁴ Gaskell: *Jour. of Anat. and Physiol.*, vol. xi, p. 720, 1877.

³⁵ Starling: Schäfer's "T. B. of Physiol.," vol. II, p. 320, 1900.

mylo-hyoid muscle, by the glosso-pharyngeal, the pharyngeal branches of the vagus, the fifth, and the spinal accessory nerves to the muscles of the fauces and pharynx." Conversely, Charles Bell obtained paralysis of the facial muscles on cutting the fifth nerve. (Quoted by Schäfer.³⁶)

When these observations are supplemented in the light of the experimental facts previously adduced, and the aggregate is taken as the basis of analysis, a close functional relationship between the muscles of the sweat glands and the skeletal muscles not only suggests itself, but the fifth nerve stands out prominently as the motor nerve of both.

Sherrington³⁷ states that "the nerves of muscles derive large numbers of their fibers from the spinal ganglia." In the limb muscles of the monkey and cat he³⁸ found "from a half to a quarter of all the nerve fibers to be sensory." He also says that "these sensory fibers end in end-organs—muscle spindles, Golgi-organs, modified Pacini-organs, and in Pacini bodies." As is well known, anaesthesia of the surface prevents the development of convulsions: it is therefore by paralyzing the cutaneous sensory *end-organs*, of nerves connected with the muscular nerve-supply that these abnormal muscular contractions are prevented. Again, while Binswanger obtained spasm reflexly—efferent motor impulses being necessary factors of the are—in various parts of the body by stimulating branches of the fifth pair, Sherrington as interpreter of the prevailing knowledge, states that the gelatinosa which caps the posterior horns and receives all the fibers from the sense organs of the body surface and muscles extends "without break *from the cranial fifth to the lowest coccygeal, inclusive.*"

The vasodilator effects observed by Dastre and Morat, Laffont, Gaskell point to the presence in the sweat and skeletal muscles of the head and neck of stricto-dilator nerves belonging to the fifth pair. In the light of the above data, it seems probable that this applies to the trunk and extremities as well.

What experimental evidence there is to show that an influx of blood into a gland is not the factor which incites function

³⁶ Cited by Schäfer: *Ibid*, vol. II, p. 726.

³⁷ Sherrington: *Ibid*, vol. II, p. 1007.

³⁸ Sherrington: *Jour. of Physiol.*, vol. XVII, p. 211, 1894.

loses considerable of its weight if the views I have submitted are sound. Howell,³⁹ for instance, writes: "The action of the nerve-fibers upon the sweat glands cannot be explained as an indirect effect—for instance, as a result of variation in the blood-flow. Experiments have repeatedly shown that, in the cat, stimulation of the sciatic still calls forth a secretion after the blood has been shut off from the leg by ligation of the aorta, or indeed after the leg has been amputated for as long as twenty minutes." An important feature of these experiments, however, is that the secretory activity is of very short duration and that the relaxation of the arterioles and the sudden influx of blood among the epithelial cells induced by stimulation of the sciatic nerve is sufficient to account for it. Howell also states that "in human beings it is known that profuse sweating may often accompany a pallid skin, as in terror or nausea." In all of these conditions, as shown in the second volume, there is general vasodilation, including of course relaxation of the arterioles, which also increases the volume of blood admitted to the epithelial cells. M. Duval⁴⁰ states that in moribund cats, while the heart-action is growing weaker, sweating of the toe-pads occurs; and if these are not pigmented they become pale and exsanguine. This corresponds with the profuse sweating of death-agony in human beings, which is also attended, of course, with pallor—an obvious sign that the vascular arterioles are relaxed allowing a temporary influx of blood into the sweat-glands. Finally, as I will show on page 1380, pilocarpine—as well as other drugs, nicotine, for example—owes its sudorific properties to the fact that it depresses the sympathetic center, thus causing relaxation of the arterioles. Yet, division of the sciatic nerve, through which the sympathetic fibers reach the arterioles of the lower extremities, does not prevent sweating in the corresponding limb. But we must not lose sight of the fact that the relaxation of all the arterioles of the body by the drug produces a condition akin to that observed in moribund animals, and that under such conditions division of the sciatic would not prevent an influx of blood into the gland and cause sweating.

The process through which the functions of a sweat-gland

³⁹ Howell: *Loc. cit.*, p. 790.

⁴⁰ Duval: "Cours de physiologie," 1892.

are influenced by variations of blood-flow becomes all the more evident when we take into account its histology and especially the manner in which the muscular elements are disposed.

In the light of all this evidence, the following conclusions seem warranted:—

1. *The secretory activity of a sweat-gland is increased by the circulation of an excess of adrenoxidase-laden plasma in its epithelial and muscular elements.*

2. *All the intrinsic structures of the gland being thus rendered hyperactive, the secreting activity of the glandular elements is enhanced and the spiral muscles around the coiled and straight tubes are caused to contract periodically, each contraction causing an outflow of sweat.*

3. *The increased supply of blood is due to dilation of the glandular arterioles by vasodilator impulses received through the secreto-motor nerve of the gland (probably an extension of the fifth including its spinal extension).*

4. *The secretory activity of a sweat-gland is reduced when the volume of blood circulating through it is decreased owing to contraction of its arterioles by vasoconstrictor impulses, received through its sympathetic terminals.*

The capillaries form a close net-work around the coiled tubes, and reach down to an extremely thin basement membrane, which, in turn, surrounds the layer of muscular fibers that coil around these tubes. An important feature of this muscular layer,—which is only separated from the cavity or lumen of the tube by the secreting epithelial cells and their endothelial lining,—however, is that its ribbon-like fibers are spirally wrapped round the tube, and in such a manner as to leave a gap between their border, throughout their whole length. Not only, therefore, is the thin basement membrane thus enabled to reach the secreting cells through the gaps, but the former actually project through the latter so as to touch the membrane. Furthermore, the projecting cells are so related to one another as to form canaliculi-like spaces, which extend from the capillary-covered membrane completely through to the lumen of the tube (Ranvier).

MAMMARY AND SEBACEOUS GLANDS.—Foster refers to the influence of the nervous system upon the mammary glands in

the following words: "That both the secretion and ejection of milk are under the control of the nervous system is shown by common experience, but the exact nervous mechanism has not yet been fully worked out. While the erection of the nipple ceases when the spinal nerves which supply the breast are divided, the secretion continues, and is not arrested even when the sympathetic as well as the spinal nerves are cut."

The nerves that supply these organs and the skin covering them are the intercostals from the second to the sixth, inclusive; the thoracic branches of the brachial plexus; and the descending branches of the cervical plexus, while sympathetic filaments accompany all blood-vessels.

In this analysis we will, in a measure, cover two subjects, since the mammary secretion is carried on in a manner similar to that which prevails in sebaceous glands. The functional process in the latter and the similarity referred to are well illustrated in the following quotations from the work of W. Roger Williams.⁴¹ Referring to the sebaceous glands, this author says: "Within the *membrana propria* of its secretory part we find a stratum of small, irregularly-shaped *epithelial cells*, each with a large nucleus (Fig. 1, *b*). The cells of this region are constantly proliferating, and, as the products of the process gradually shift *toward the duct*, they become changed and gradually form the secretion." If the words that we have italicized are placed in immediate sequence, they will be found to describe exactly the histological arrangement of the sweat-tubes from the delicate membrane to the lumen. "The steps of the process are as follows: The cells next the marginal cells (Fig. 1, *b*) increase in size and their nuclei dwindle. As they approach the center of the acinus their nuclei disappear, and the cells become distended with granules and oil-globules. Finally they burst and their *débris* forms the secretion, which is discharged." This also coincides with the manner in which sudoriferous glands produce their secretion.

"Lactation is the outcome of a similar process," continues Mr. Williams. "Milk must, therefore, be regarded as the product of the deliquescence of successive degenerations of epithe-

⁴¹ W. Roger Williams: "Diseases of the Breast," London. 1894.

lial cells which are destroyed in this process and replaced by relays of new cells derived by division from other still active epithelial cells of the part. Thus we see that growth, development, and secretion are but slightly varied manifestations of cellular activity finding expression in different ways." . . . "The complete degree of mammary function that eventuates in lactation is only attained periodically, and the process is always gradual. The following is a brief account of Creighton's description of it: Subsidence of the function goes hand in hand with undoing of structure, and revival of the function with the building up of structure. Variations of intensity in the secretory force are measured by its products

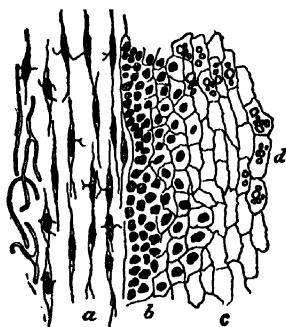


FIG. 1.—HISTOLOGICAL SECTION OF THE WALL OF A SEBACEOUS CYST. (Cornil and Ranvier.)

a, Fibrous stratum with connective tissue corpuscles. *b*, Marginal stratum. *c*, Hornifying cells. *d*, Sebaceous cells.

which correspond to changing aspects of the secreting acini. The beginning of the rising function coincides with the beginning of pregnancy, and the process occupies the entire period of gestation. During the intervals between its periods of functional activity the breast remains in a quiescent functionless state: the *resting* stage. In this condition the gland is shrunk and surrounded by a considerable quantity of fibro-fatty tissue. The acini are shriveled up. On microscopical examination of sections of the gland in this stage (Fig. 2) each acinus appears as an alveolar space bounded by a thin layer of fibrous tissue, denuded of epithelium. Its con-

tents are irregularly-arranged, polymorphic, epithelial cells, with large nuclei and scanty surrounding protoplasm. . . .

"During the *rising* function the size of the acini gradually increases from that of the resting stage. The cells increase in number and size and acquire more protoplasm. They gradually arrange themselves so as to form a lining membrane for the wall of the acinus (Fig. 3), which, as lactation approaches, is converted into a regular mosaic. The cells become granular, irregularly shaped, excavated, and vacuolated, secreting granular and mucous fluids. The milk of the first few days is always somewhat crude, containing colostrum-cells, which



FIG. 2.

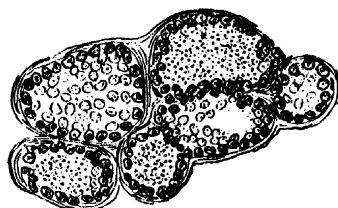


FIG. 3.

THE MAMMARY LOBULE NEAR THE RESTING STAGE (UPPER) AND DURING FUNCTIONAL ACTIVITY. (Creighton.)

are the last of the long series of secretory products thrown off during the period of rising function.

"The fully-expanded acinus (Fig. 4) in a state of active secretion is at least four times as large as that of the resting stage. Its contained cells are much more numerous than at any other period, and they form a perfect mosaic, lining the membrana propria. Each cell is flattened and of polyhedral shape, and has a large nucleus surrounded by a broad zone of protoplasm.

"During the period of subsiding function the organ gradually reverts to the resting stage through the converse series

of changes. In this process the cells pass through a succession of transformations, from the forms characteristic of the perfect mosaic of lactation to those peculiar to the various stages of the subsiding process. These changes are accompanied by constant destruction and renewal of the participating cells.

"With regard to the influence of the nervous system on the mammary secretion, most of those who have studied the subject are agreed that the secretion of milk is not directly under its control. Laffont,⁴² however, maintains that the mammaræ possess *vasodilator* nerves which, *when stimulated*, cause augmentation of the quantity of milk secreted; but de Sinéty,⁴³ who has repeated his experiments, is unable to accept his conclusions."

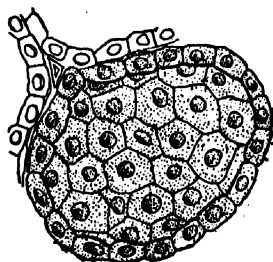


FIG 4.—EXPANDED MAMMARY ACINUS, SHOWING THE ARRANGEMENT OF EPITHELIAL MOSAIC. (*Ureighton*.)

The foregoing review not only indicates the important part cellular metabolism plays in the functions of the mammary glands, but also that the blood is an important source of active functional work. "The blood is the ultimate source of milk," says Foster, "but it becomes milk only through the activity of the cell, and that activity consists largely in a metabolic manufacture by the cell, and in the cell, of the common things brought by the blood into the special things present in the milk. Experimental results tell the same tale." Another feature which it places on a solid footing when asso-

⁴² Laffont: *Comptes-Rendus de l'Académie des Sciences*, vol. lxxxix, 1879.

⁴³ De Sinéty: *Mémoires de la Société de Biologie*, vol. 1, 1879.

ciated with Professor Foster's remark, and one which I wish particularly to emphasize, is the identity of the liquid which holds the various constituents of milk in solution, viz.: blood-plasma. This is also suggested by a statement of M. Duval's, who, referring to the formation of cream, says: "The transparent portion that remains at the bottom of the vessel represents the plasma of the milk: that is to say, the milk without globules. We employ the word 'plasma' here to establish a parallelism between the analysis of milk and that of the blood. Skimmed milk corresponds to the liquor of the blood."

In another chapter the true identity of blood-plasma, owing to its inherent oxidizing substance or adrenoxidase, its antitoxin, etc., as a prophylactic, and its rôle in this connection, will be further studied. But, bearing directly upon the question in point,—i.e., the functional mechanism,—the presence of plasma in the milk forcibly indicates that an important vasoconstrictor system must exist in the mammary gland. In fact, that so careful an investigator as Laffont should have observed vasodilation further emphasizes this, and tends to indicate that a process similar to that described by me in my analysis of submaxillary functions must prevail,—i.e., *indirect* vasodilation,—a fact sustained by the counter-experiments of an equally competent physiologist, de Sinéty, who was unable to find vasodilators *per se*. Laffont reached his deduction that vasodilation occurred by measuring the blood-pressure in the mammary artery of a bitch, during lactation, after severing the mammary nerve and stimulating the peripheral segment of the latter. Congestion of the gland and increase of milk-flow followed, but after cessation of the artificial stimulation the flow, though not arrested, was greatly reduced. This led Laffont to conclude inferentially that the mammary gland possessed typical vasodilators similar to those thought to exist in the submaxillary gland. I have shown that the phenomena upon which such a deduction could be based, in respect to the latter organ, could be accounted for without vasodilators and that active dilation was a mechanical impossibility. Claude Bernard's own testimony to this is indirectly afforded by the fact that the "interference" or "inhibition" theory was introduced by him to account for vasodilation: the existence of which he was

first—as he had been in the case of vasoconstriction—to demonstrate.

The various data reviewed seem to me, when considered collectively, to suggest modifications of generally accepted views. In the mammary gland the secreting apparatus is formed, we have seen, first by an extremely thin basement membrane, and, second, by a single layer of epithelial secretory cells. The latter supply the milk-forming elements other than the liquid *per se*, which liquid responds to various tests of blood-plasma (Duval) and seems to replace the water secreted by the sweat, salivary, and lacrymal glands. In all three of the latter organs, however, the secreting structures are surrounded by a net-work of capillaries. That such is also the case in the mammary gland is evident, since Piersol,⁴⁴ referring to the glandular vessels, says: "From these vessels on the anterior surface of the organ branches penetrate into the glandular mass and pass between the lobules, giving off twigs which break up into capillaries inclosing the alveoli." A net-work of nerve-filaments are also traced to the glandular elements of salivary and sudoriferous glands: a feature also reproduced in the mammae. Thus, Böhm and von Davidoff,⁴⁵ alluding to the terminations of the nerves in the mammary glands, recall that they have been studied by means of the methylene-blue method by Dmitrewsky, who found that "the terminal branches form epilamellar plexuses outside the basement membrane of the alveoli, from which fine nerve-branches pass through the basement membrane and end on the gland-cells in clusters of terminal granules united by fine filaments." They also state that "the vessels form capillary net-works surrounding the alveoli." The ducts when nearing the nipple have an outer layer of cellular tissue containing a large number of elastic fibers and smooth muscular fibers which depart slightly from the axial line in direction, though insufficiently so to be termed "spiral" as in the case of the sweat-gland muscles. But, in the mammary gland, suckling, by creating a vacuum and causing elongation of the nipple, fulfills the function of the latter.

⁴⁴ Piersol: "Normal Histology," p. 241, seventh edition, 1900.

⁴⁵ Böhm and von Davidoff: "Text-book of Histology," translated by Huber, p. 361, 1900.

We thus have all the structural elements of the previously studied glands present in these. Their peripheral mechanisms should also correspond, however. As to the nervous supply, we have seen that dilation of arteries was found to be controlled by motor nerves, by Laffont, and that the presence of vasomotors was denied by de Sinéty. Hence, the vasodilation must be due to indirect action, especially since Laffont caused it by stimulating these nerves, precisely as Claude Bernard had done in the case of the submaxillary glands. The stimulation must, therefore, have caused this indirect vascular dilation in the manner described when the chorda tympani was in question: *i.e.*, by causing stricto-dilation of the glandular vessels. That this conception of the process is justified is further sustained by the experiments of Rohrig,⁴⁶ who found that a *motor* nerve, the external spermatic, supplied constrictor fibers to the glandular blood-vessels in the goat, and that division of *one branch* of this nerve, the lower, enhanced secretion (evidently due to relaxation of the vessels through loss of their normal stimulus), while stimulation of the peripheral end of this subdivision of the nerve decreased the secretion. This clearly suggests that, just as is the case in the submaxillary and other glands, the secretory activity of the organ should be attributed to an increase of the blood coursing through its secretory elements.

As to the sympathetic fibers, they are also stated by Roger Williams to "accompany the mammary blood-vessels"; and, as section of a sympathetic nerve is always followed by dilation of the arteries, they can only act as vasoconstrictors here as elsewhere. That all efferent fibers distributed to the glandular elements and to the blood-vessels originate from the central nervous system is evident when their relationship with the cord, and particularly the results of section immediately below the medulla, are recalled. That a single stream of impulses from the cerebral centers can sustain the entire function—that is to say, that part of it under nervous control—scarcely needs, under these conditions, to be emphasized.

An important characteristic of the functions of the mam-

⁴⁶ Rohrig: *Virchow's Archiv*, vol. *lxvii*, 1876.

mary glands, however, is that their dependence upon their nervous supply is not as great as is the case with other organs. This is readily accounted for when the identity of the liquid portion of milk is realized. The blood-plasma must undergo but little change during its conversion into milk-plasma; indeed, it is probably merely filtered through the membrana propria and the epithelial layer of cells in the lobules and thus becomes charged with their products. Leucocytes are the main source of the latter; Kadkin⁴⁷ found them both in the epithelial lining and alveolar cavities, "wherein disintegration of their nuclei supplies the milk with a proportion of its nuclein, the remaining amount of the latter being furnished by the epithelial cells." These bodies and the oxidizing substance of the blood-plasma not only transfer to the milk their immunizing qualities, but the oxidizing substance is itself a source of functional energy through which leucocytes and epithelial cells are caused to endow the milk with its nutritive principles. Much of the organ's work is therefore automatic.

While "the secretion continues and is not arrested even when the sympathetic as well as the spinal nerves are cut," control experiments soon show that, as was the case with Laffont's animal, the flow, though not arrested, is reduced even when only one set of nerves is cut. This indicates, when considered along with the fact that stimulation of the mammary end of the nerve increases the gland's activity, that the nervous supply must not be disregarded, and it also suggests that the sharp line drawn between "active" and "passive" activity, in the case of other organs, and which mainly depends upon nerve-impulses to secreting structures and vascular walls, is scarcely applicable here. Indeed, we are doubtless dealing with mere fluctuations of activity, called forth, during lactation, by afferent impulses to the motor centers: a feature which the rapid formation of milk after nursing and the influence of emotions upon its flow suggest. In framing our summary of the functional mechanism of the mammary gland, therefore, it is not the difference between active and passive activity that we have in mind, but the manner in which fluct-

⁴⁷ Kadkin: Inaugural Dissertation, 1890.

uations of activity are brought about. The actual process involved, even here, however, is primarily a mechanical one, since filtration of the blood-plasma into the secreting elements represents no mean expense of force. As blood-pressure totally independent of the normal systemic pressure must account for this, we are relegated to the vessel-walls and their nerve-supply as the intermediaries through which this is carried out.

On the whole, the functional mechanism of a mammary gland may, in the light of the foregoing facts, be interpreted as follows:—

1. *The formation of milk is due to an exacerbation of secretory activity, the nutrient fluid being held in reserve by the organ until withdrawn mechanically by the suckling.*

2. *Blood-plasma, including its oxidizing substance (adrenoxidase), is the main fluid constituent of milk, and is supplied to the secretory cells by the glandular arterioles when these vessels are dilated by their motor nerves, the terminals of the fourth, fifth, and sixth intercostals.*

3. *When the formation of milk is to cease, the arterioles referred to resume their normal caliber, the result of constrictor impulses received through the intermediary of their sympathetic nerves.*

KIDNEYS.—Howell⁴⁸ states that “the kidneys receive a rich supply of nerve-fibers,” but that “most histologists have been unable to trace any connection between these fibers and the epithelial cells of the kidney tubules.” Interpreted from my standpoint such a connection is not in the least necessary, since as I have now shown repeatedly, the function of an organ is dependent upon the volume of arterial blood circulating through it. My view is fully sustained by the prevailing doctrine, since, as Howell says, the marked effects obtained during purely physiological experiments are “all explicable by the changes produced in the blood-flow through the organ.” It becomes a question, therefore, as to how, and by what nerves this blood-flow is regulated, for as stated by Stewart⁴⁹ “increased blood-flow entails increased secretion.”

⁴⁸ Howell: T. B. of Physiol., second edition, p. 763, 1907.

⁴⁹ Stewart: Loc. cit., p. 419.

That the vasodilation necessary to the inception of an exacerbation of function—as it is in the submaxillary gland—occurs in the kidney as well as in the organs previously reviewed, is shown by the experiments of Bradford⁵⁰ who found that vasodilator nerves entered the kidney with the vasoconstrictor fibers, and that when the anterior roots of the eleventh, twelfth, and thirteenth dorsal nerve roots were stimulated with induction shocks one second apart, the organ swelled though no sufficiently marked rise of blood-pressure occurred to account for it. Stewart⁵¹ also states that the presence of dilator fibers for the kidney has been “demonstrated in the splanchnic nerves.” That it is these vasodilators which enhance the flow of urine is sustained by the prevailing opinion that true secretory nerves, *i.e.*, nerves influencing directly the epithelial elements, are not present in the kidney.

The source of these renal vasodilator nerves is disclosed by the fact that it is only by stimulating the splanchnic that the caliber of the renal arteries is increased. Indeed, Eckhard⁵² found that stimulation of the vagi below the diaphragm does not influence the flow of urine. This imposed the conclusion that even the vasodilators of the kidney belong to the sympathetic system. This is confirmed by the researches of Berkley⁵³ which showed that “the innervation of the kidney is dependent directly upon the great sympathetic; and histologically speaking, it is found that all the nerves of the glands belong to the non-medullated type.” Briefly, the vasodilator nerves of the kidney which promote the flow of urine belong to the sympathetic system.

How are the arteries restored to their normal caliber—that compatible with the normal excretion of urine?

In the light of the conclusions submitted in the foregoing pages the kidneys should receive filaments capable of causing constriction of the renal arteries when the excretory activity of the organs is to be decreased. That such is the case has been shown experimentally by many observers. In the dog, the

⁵⁰ Bradford: *Jour. of Physiol.*, vol. x, p. 358, 1889.

⁵¹ Stewart: *Loc. cit.*, p. 152.

⁵² Eckhard: Cited by Starling: Schäfer's “*T. B. of Physiol.*,” vol. i, p. 645.

⁵³ Berkley: *Jour. of Path. and Bact.*, vol. i, p. 406, 1893.

vasoconstrictor nerves leave the cord, according to Stewart, "by the anterior roots of the sixth thoracic to the second lumbar nerves and especially the last three thoracic." Langley⁵⁴ observed prompt and great pallor of the kidney and upper part of the ureter on stimulating the first lumbar nerve, and slower, though still great, pallor on stimulating the second lumbar in the cat. As stated by Starling⁵⁵ a rise of the general blood-pressure coincides with marked shrinkage of the kidney, so that the effects observed by Langley must be of vasomotor origin. Moreover various toxics known to raise the vascular pressure produce effects similar to stimulation of the renal vasomotor nerves. Thus Sakussow⁵⁶ recently found that digitalin in 1 to 1,000,000 solution caused contraction of the renal vessels. The same effect was obtained from a 1 to 1,000,000 solution of adrenalin. The latter result accounts for the fact that Bradford⁵⁷ obtained renal vasoconstriction by stimulating, besides the nerves included within the above limits, the fourth and fifth thoracic, thus including among those stimulated, the fibers which pass to the splanchnic and thence to the kidneys. He found, however, that the most active vasomotor nerves were those of eleventh, twelfth, and thirteenth thoracic. That all these filaments are distributed to the arterioles in the organs has not only been established histologically, but as stated by Böhm, Davidoff, and Huber,⁵⁸ "from the plexuses surrounding the vessels small branches are given off which end on the muscle-cells of the media.

As to the source of the vasoconstrictor fibers, it corresponds with that of the vasoconstrictors supplied to other abdominal organs, the splanchnic. Thus Nollner⁵⁹ and others have traced these nerves from the sympathetic chain through the great and small splanchnics to the solar plexus, and thence to a network of fibers lying in the fat between the adrenal and the kidney. Several of the filaments were found by Nollner to enter the latter with the renal artery.

⁵⁴ Langley: Schäfer's "T. B. of Physiol.," vol. II, p. 645.

⁵⁵ Starling: *Ibid.*, vol. I, p. 645.

⁵⁶ Sakussow: *Vratch*, April 10, 1904.

⁵⁷ Bradford: *Jour. of Physiol.*, vol. X, p. 358, 1896.

⁵⁸ Böhm, Davidoff and Huber: *Loc. cit.*, p. 335, 1905.

⁵⁹ Nollner: *Beiträge z. Anat. u. Physiol. v. Eckhard*, Bd. IV, S. 139, 1899.

We thus find ourselves in the presence of the surprising fact that both the vasodilator and vasoconstrictor nerves of the kidneys—those which preside over the functions of these organs, are of sympathetic origin. Indeed, as will be shown later, this is a characteristic of the adrenals, these organs and the kidneys working in harmony: the adrenals by supplying, as we have seen, the oxidizing substance of the blood, which takes part, among other functions, the disintegration or proteolysis of waste-products in order to convert them into eliminable end-products; the kidneys, by insuring the excretion of these end-products from the system.

This accounts for various observations that present knowledge fails to explain. Thus Aubertin and Ambert⁶⁰ found concomitant lesions, both on naked eye and microscopical examination, in the adrenals and kidneys in all cases of nephritis studied by them characterized by high-pulse tension. The latter phenomenon suggests that while an excess of adrenal secretion was being produced—this product and adrenalin causing, as is well known, a marked rise of the vascular tension—the kidneys had also been overworked in these cases, *i.e.*, excessive excretory activity had brought on the nephritis. In other words, marked increased functional activity of the kidneys, as represented by renal vasodilation, should coincide—since the adrenals are simultaneously stimulated—with increased vascular tension. This has been actually observed experimentally by Cavazzani,⁶¹ though unexplained by him. He found that urea caused simultaneously expansion of the kidney—and therefore an increased production of urine—and general vasoconstriction. Puncture of the floor of the fourth ventricle (Bernard's *piqûre*) produces glycosuria through the intermediary of the adrenals, as will be shown elsewhere; a similar puncture also produces, as stated by Stewart, "a copious flow of urine." We need not go beyond common experience to find ample proof of the fact that polyuria is a prominent symptom of diabetes, *i.e.*, that the adrenals and the kidneys work in harmony. The importance of this relationship asserts itself when the obscurity surrounding the question is recalled. Thus referring to polyuria, Hensell,

⁶⁰ Aubertin and Ambert: *Tribune médicale*, p. 119, 1904.

⁶¹ Cavazzani: *Arch. ital. de biol.*, vol. xviii, p. 158.

Well, and Jelliffe⁶² state that "it is common to two diseases—diabetes mellitus and chronic interstitial nephritis—but in either case a clear explanation of this symptom does not exist."

Pending additional evidence to this effect the following conclusions as to the functions of the kidney appear to us warranted:—

1. *When the flow of urine is to be increased, the renal arterioles are dilated by vasodilator terminals of the sympathetic which reach the organ by way of the splanchnic nerves and the semilunar ganglia. The glomerular tufts being thus traversed by a greater volume of blood the components of urine are thus filtered out into Bowman's capsule.*

2. *When the flow of urine is to be decreased the same arterioles are reduced to their normal caliber by the vasoconstrictor filaments of the sympathetic which reach the kidneys also by way of the splanchnic nerves.*

4. *The adrenals and the kidneys are functionally united, the adrenals contributing by their secretion to the conversion of waste-products into end-products which the kidneys excrete with the urine.*

With the functions of the kidneys as complementary to those of the adrenals, what we have termed the "adrenal system" acquires greater importance in the vital functions of the organism as a whole: it supplies the body the substances which sustain oxygenation and metabolism, but provides also for the elimination of end-products of catabolism and other wastes. By "substances" here, are meant both the adrenal and thyroid secretions. The former of these, by becoming oxygenized in the lungs, constitutes the oxidizing substance of the blood, *i.e.*, the albuminous portion of its hæmoglobin; the thyroid secretion as previously stated, and as will be shown, enhances the vulnerability of all tissues to oxidation, including the adrenal center in the pituitary body.

As to the functional relationship between all these organs, they may be briefly summarized as follows, pending additional evidence:—

The pituitary body contains a center which governs the

⁶² Hensel, Well and Jelliffe: "The Urine and Fæces," 1905.

functional activity of the adrenals and of the kidneys. Any excitation of this center by certain toxics that may occur in the blood increases the functional activity of both the adrenals and the kidneys, and, therefore, general oxygenation and renal excretion.

THE INTERNAL SECRETION OF THE KIDNEY.—The belief that the kidneys are the source of an internal secretion dates back to 1869, when Brown Séquard showed that injections of renal extract postponed the development of uremia in nephrectomized animals, and prolonged life. Lépine found in addition that a filtrate of a watery extract of kidney caused a rise of temperature and dyspnea. Moreover, Oliver and Schäfer showed in 1898 that a cold-water extract of fresh kidney, when injected intravenously in rabbits, soon produced a more or less marked rise of the blood-pressure. All these observations have been amply confirmed.

In the light of the data I have adduced, however, none of the above phenomena can be attributed to a renal internal secretion: They represent merely the effects of extracts of adrenal rests contained in the kidney substance, and of which adrenoxidase the blood in the renal tissue used in the preparation of the extracts happened to contain. The existence of adrenal rests is the recognized source of hypernephromata (see page 129); indeed, Lewandowsky found that the effects obtained from renal venous blood differed in no way from corresponding quantities of venous blood obtained elsewhere in the body. As to the rise of temperature, the elevated blood-pressure, and the dyspnea, they are all typical effects of adrenal extracts. Fuchs and Roth⁶³ found that adrenalin increased markedly the intake of oxygen and the output of carbon dioxide, while Reichert, Lépine, and Morel noted that adrenal extracts increased the temperature along with the blood-pressure. Oliver and Schäfer not only demonstrated the latter phenomenon, but also the fact that adrenal extracts produced dyspnea and could even arrest respiration. This observation which was recently confirmed by Langlois and Garrelon, is obviously due to toxic spasm of the respiratory muscles, the precursor of the convulsions witnessed. As to the benefit obtained with renal extracts, they were simply due to the detoxicatory

⁶³ Fuchs and Roth: *Zeitsch. f. Pathol. u. Ther.*, B. x, p. 187, 1912.

action of the adrenal principle first pointed out by Landois and now generally recognized. On the whole, the following conclusion seems to me warranted.

No internal secretion of the kidney exists; all effects of renal extracts witnessed are due to the adrenal principle the kidney normally contains.

GENERAL CONCLUSIONS AS TO THE MECHANISM OF FUNCTIONAL ACTIVITY.—Pending additional evidence the following deductions regarding the several organs studied so far appear warranted:—

1. *The arterioles of the skeletal muscles and of the lacrymal, salivary, sweat, and mammary glands receive the terminals of two kinds of nerves: a, motor or secreto-motor fibers supplied by a cranial nerve; b, constrictor fibers supplied by the sympathetic system.*

2. *The terminals of the cranial nerves cause the arterioles of these organs to dilate and to admit an excess of blood, i.e., of oxidizing substance (adrenoxidase), into them, thus enhancing their functional activity.*

3. *When this exacerbation of functional activity is to cease, the sympathetic fibers cause the arterioles to contract until they resume their normal caliber.*

4. *The functions of the kidney are carried on in the same way, but this organ differs from those enumerated above in that both its vasodilator and vasoconstrictor nerves are supplied by the sympathetic system.*

Again, the data submitted suggest that the red corpuscles are not distributors of oxygen, but the carriers of oxidizing substance which they supply to the blood-plasma. It is this plasma which, after traversing the walls of the capillaries—leaving behind it the red corpuscles—penetrates to the tissues and activates their epithelial elements by means of its oxidizing substance.

On the whole, the conclusion seems warranted that

5. *In all the above-mentioned organs the oxidizing substance (adrenoxidase)—a combination of adrenal secretion and oxygen formed in the lungs and of which the red corpuscles and the blood-plasma are the vehicles—is the physico-chemical agency through which cellular metabolism is sustained during PASSIVE functional activity, and increased during ACTIVE functional activity.*

CHAPTER VII.

THE ADRENAL SYSTEM IN THE FUNCTIONS OF THE DIGESTIVE ORGANS.

THE ADRENOXIDASE AND THE DUAL NERVOUS SUPPLY OF THE ORGANS OF DIGESTION.

THE oxidizing substance, or adrenoxidase, has now been shown to subserve the needs of several sets of organs; we will now find it to assume similar functions in the stomach, liver, heart, lungs, etc., notwithstanding the dissimilarity of the functions of these organs. Here, again, the uncomplicated nervous functions I have described—all apparently carried on, as far as efferent impulses are concerned, through the agency of a motor, *i.e.*, vasodilator and a sympathetic vasoconstrictor—suffice, the gastric vasodilator being, however, the pneumogastric or vagus.

THE STOMACH AND ITS PHYSICO-CHEMICAL FUNCTIONS.—

In an able review of the relationship between the nervous system and the production of gastric secretion Howell¹ introduces the following remarks: "It has been very difficult to obtain direct evidence of the existence of extrinsic secretory nerves to the gastric glands. In the hands of most experimenters stimulation of the vagi and of the sympathetics has given negative results, and, on the other hand, section of these nerves does not seem to prevent entirely the formation of the gastric secretion. There are on record, however, a number of observations that point to a direct influence of the central nervous system on the secretion. Thus, Bidder and Schmidt found that in a hungry dog with a gastric fistula the mere sight of food caused a flow of gastric juice, and Richet reports the case of a man in whom the œsophagus was completely occluded and in whom a gastric fistula was established by surgical operation: It was then found that savory foods chewed

¹ Howell: "American Text-book of Physiology," second edition, 1900.

in the mouth produced a marked flow of gastric juice. There would seem to be no clear way of explaining the secretions in these cases except upon the supposition that they were caused by a reflex stimulation of the gastric mucous membrane through the central nervous system."

The Gastric Nervous Supply and the Formation of Gastric Juice.—When the nervous supply of the stomach is closely examined, a rather unusual state of affairs presents itself: *i.e.*, it contains no *bona fide* motor nerves, unless we grant the many sympathetic fibers distributed to it motor qualities, or, refusing to recognize these, accept the vagus as the secretory nerve. But, if we do this, to which nerve must we ascribe the afferent impulses, which the ingestion of various substances that cause nausea and other manifestations which clinicians so often witness induces? The sympathetic has everywhere shown itself as an efferent nerve, and I have already furnished considerable evidence in favor of my view that sympathetic nerves serve to constrict the arterioles after these vessels have been dilated by vasodilator nerves. We can thus account for the phenomena witnessed and relegate also to the vagus the rôle of afferent nerve; thus construed, its impulses to the vagal center evokes therefrom secretory impulses to the gastric mucosa.

Howell, continuing the remarks quoted above, says: "These cases are strongly supported by some recent experimental work on dogs by Pawlow and Schumowa-Simanowskaja. These observers used dogs in which a gastric fistula had been established, and in which, moreover, the œsophagus had been divided in the neck and the upper and lower cut surfaces brought to the skin and sutured so as to make two fistulous openings. In these animals, therefore, food taken into the mouth and subsequently swallowed escaped to the exterior through the upper œsophageal fistula without entering the stomach. Nevertheless, this 'fictitious meal,' as the authors designate it, brought about a secretion of gastric juice. If in such animals *the two vagi* were cut, the 'fictitious meal' no longer caused a secretion of the gastric juice, and this fact may be considered as showing that the secretion obtained when the vagi were intact was due to a reflex stimulation of the stomach

through these nerves. In later experiments² from the same laboratory the secretion caused in this way by the act of eating is designated as a 'psychical secretion,' on the assumption, for which considerable evidence is given, that the reflex must involve psychical factors, such as the sensations accompanying the provocation and gratification of the appetite. In favorable cases the fictitious feeding was continued for as long as five to six hours, with the production of a secretion of about 700 cubic centimeters of pure gastric juice. Finally, these observers were able to show that *direct stimulation of the vagi*³ under proper conditions causes, after a long latent period (four and a half to ten minutes), a marked secretion of gastric juice. The long latent period is attributed to the simultaneous stimulation of inhibitory fibers." Howell closes his review of this subject by the remark: "Taking these results together we must believe that the vagi send secretory fibers to the gastric glands, and that these fibers may be stimulated reflexly through the sensory nerves of the mouth, and probably also by psychical states."

Indeed, Pawlow in collaboration with Madame Schumow-Simanowski⁴ demonstrated conclusively that the vagus was the secretory nerve of the stomach. They obtained no secretion by exciting the splanchnics, while stimulation of the peripheral ends of the cut vagi gave positive results, even twenty-four hours after the nerves had been divided. Schneyer⁵ confirmed these observations. Stimulation of the vagus in the neck produced a secretion chemically and physiologically similar to gastric juice. Stimulation of any portion of the splanchnic failed to do so. The experiments of Rutherford⁶ pointedly suggest the strieto-dilator action of the vagus. Having cut both vagi during digestion he noted that the mucous membrane became paler; on stimulating the cut fibers connected with the organ the membrane became hyperæmic.

² Pawlow and Schumowa-Simanowskaja: "Die Arbeit der Verdauungsdrüsen," Wiesbaden, 1898.

³ All italics are our own.

⁴ Pawlow and Schumow-Simanowski: "The Work of the Digestive Glands," by Pawlow, St. Petersburg, 1897; transl. by W. H. Thompson, 1902.

⁵ Schneyer: Zeit. f. klin. Med., Bd. xxxii, Nos. 1 and 2, S. 131, 1897.

⁶ Rutherford: Trans. of Royal Soc. of Edinburgh, vol. xxvi, 1870.

The identity of the vagus as the gastric secreto-motor nerve being established, another feature of especial interest is its power to provoke the muscular contractions it governs. Morat⁷ observed that the movements of the stomach could be arrested reflexly by stimulating the central end of the vagus. Kronecker and Meltzer⁸ noted a similar phenomenon. Wertheimer⁹ reached the same results by stimulating the central end of the sciatic. Openchowski,¹⁰ however, obtained direct relaxation of the cardiac orifice by stimulating a nerve formed by filaments derived from both vagi, and overlying this part of the organ. Langley¹¹ among other investigators, repeated Openchowski's experiments and confirmed his results. After "connecting the œsophagus with a vertical tube containing fluid at a pressure of 15 to 20 centimeters water pressure and stimulating the peripheral end of the vagus after curari and atropine had been given" he writes "the sphincter opens and fluid passes into the stomach." He also ascertained experimentally that the body of the stomach and the pylorus receive inhibitory as well as motor fibers from the vagus." As the vagal fibers can relax the gastric orifices when ingesta are to pass through them, and, in the case of the pylorus, only when they are fit to pass, we are dealing, in *vagal* inhibition, with a physiological function, whereas sympathetic "inhibition," as we have seen, can only be artificial.

Thus, besides its rôle as secretory nerve, the vagus also governs the stomach's motor functions, *i.e.*, its movements and contractions during digestion. This dual rôle is well illustrated by the observations of Reynard and Loye¹² in a decapitated criminal. They stimulated the vagus forty-five minutes after the execution and not only obtained the characteristic movements of the stomach, but numerous drops of gastric juice appeared on the gastric mucous membrane. On the other hand, W. P. May¹³ showed experimentally that "the splanchnic nerves

⁷ Morat: *Lyon médical*, T. xl, p. 289, 1882.

⁸ Kronecker and Meltzer: *Archiv f. Anat. u. Physiol.*, S. 328, Suppl. 1883.

⁹ Wertheimer: *Archives de physiol. norm. et pathol.*, p. 379, 1892.

¹⁰ Openchowski: *Loc. cit.*

¹¹ Langley: *Jour. of Physiol.*, vol. xxiii, p. 407, 1898.

¹² Reynard and Loye: *Comptes-Rendus de la Soc. de biologie*, p. 433, 1887.

¹³ W. P. May: *Jour. of Physiol.*, June 30, 1904.

have no direct influence whatever, either motor or inhibitory on the muscular wall of the stomach" thus showing that the sympathetic was not the stomach's motor nerve.

The sympathetic system is represented in the stomach as it is elsewhere. While Langley¹⁴ includes both the glands and the muscular coat of this organ among the structures supplied with a double nerve supply, *i.e.*, cranial and sympathetic, Rutherford¹⁵ found that "normal secretion occurred after division of the splanchnics." This points to the correctness of my view that in the stomach as elsewhere, the sympathetic terminals act as vasoconstrictors, since their division must under these circumstances produce exactly the effect noted, the resulting relaxation of the gastric arterioles bringing about the condition through which the secretory nerve, the vagus, incites normal secretion, *i.e.*, vasodilation.

The arterial distribution also sustains this view. As to Auerbach's plexus, we know that after piercing the external serous coat of the stomach its nerves pass between the circular and longitudinal muscular layers, where they form a close network strewn with ganglia, the whole constituting the plexus. The terminal fibers of this plexus are distributed as is usual in muscles: they form in the muscular coat of the stomach an *intramuscular plexus which entwines*, as it were, *the muscular fibers*. Furthermore, this plexus gives off filaments which, entering deeper into the wall of the stomach, form another plexus, also containing many ganglia: *i.e.*, Meissner's plexus. This net-work of sympathetic elements—fibers, ganglia, cells, etc.—lies in the submucous coat,—*i.e.*, immediately under the muscularis mucosæ, which separates the latter from the secretory glands. Besides the many filaments it distributes to the thin submucous muscular layer, it gives off a large number that penetrate this layer. These, on reaching the glands, form a close net-work in the connective-tissue sheath surrounding them, which net-work gives off delicate fibrils that enter into the glandular elements themselves. They likewise supply terminal fibers to the neighboring muscular elements and to their vascular supply.

¹⁴ Langley: Schäfer's "T. B. of Physiol.," vol. II, pp. 692 and 693, 1900.

¹⁵ Rutherford: *Loc. cit.*

The blood-vessels of the stomach are distributed in a very similar manner. Piersol¹⁶ describes them as follows: "The larger arteries, after penetrating the outer coats, divide within the submucosa into smaller branches, one set of which pierces the muscularis mucosæ, to be distributed to the mucous membrane, while the other enters the muscular and serous tunics. The vessels supplying the mucosa form a rich *subepithelial capillary net-work as well as mesh-works surrounding the gastric glands*, the capillaries lying immediately beneath the basement membrane in close proximity to the glandular epithelium. The branches distributed to the outer layers form long-meshed capillary net-works from which the muscle-bundle and fibrous tissue derive their supply." A feature that requires emphasis in this connection is the manner in which the vessels are finally distributed to the mucous membrane: The small arteries or arterioles do not themselves ascend between the glands, but give off fine capillaries that do so. These, by anastomosing with one another, form a very rich plexus which surrounds each glandular tubule in a net-work of close hexagonal meshes. The cellular secreting elements of the glands being covered by a *delicate basement membrane*, the capillaries are thus related to the former precisely as we found them to be in the sweat-glands. Indeed, if the intrinsic structures of the stomach are compared with those of the organs reviewed, it soon becomes evident that the mechanism to which the production of *secretions* is due does not differ from them.

We cannot, however, say the same in respect to the extrinsic vessels and nerves, and to this feature of the process we wish to call especial attention. As is well known, the vascular supply of the stomach is made up of the gastric, pyloric, and right gastro-epiploic branches of the hepatic artery and the left gastro-epiploic and vasa brevia from the splenic. The important feature referred to is this: The gastric, hepatic, and splenic arteries arise from the celiac axis, and, as shown in the earlier chapters, *the celiac axis is the first great arterial trunk to receive the blood from the lungs: i.e., before the activity of the oxidizing substance in the downward blood-stream has*

¹⁶ Piersol: "Normal Histology," p. 166, 1900.

in any way been reduced. Another very suggestive feature is that *the celiac axis is surrounded by the celiac plexus, a portion of the solar plexus of the sympathetic*, and that extensions of the celiac plexus—the gastric, hepatic, pyloric, gastro-duodenal, and gastro-epiploic plexuses—follow the arteries of the same name *to the walls of the stomach*. We thus have as the co-ordinators of gastric function, the two nerves which we found elsewhere to fulfill similar rôles, viz., the vagus, to carry on the secretory and motor functions of the stomach, and sympathetic plexuses and nerve so distributed as to constrict the blood-vessels supplied to the organ and to reduce the volume of blood circulating in its glands and muscular walls, when, after the digestive process is ended, the stomach must be restored to the passive state.

Another feature requiring our attention is the formation of the gastric secretion. In the blood-plasma we have sodium and potassium chlorides; in the secretion of the stomach these represent the most important and abundant salts, and constitute the source of the hydrochloric acid in the gastric juice, according to prevailing views. Has the oxidizing substance of the plasma any influence upon the formation of this acid? The marked affinity of chlorine for hydrogen seems able to fill the want. It takes it up whether the gas be free or in vulnerable combination *extra corpore*; it doubtless does the same in the gastric structures. But here conditions are especially well adapted for such a reaction, if we analyze the question with the aid of thermochemistry. Equal volumes of chlorine and hydrogen can only be kept in an absolutely dark place; diffuse light causes them to slowly unite, while a bright light—sunlight, for instance—brings on such an instantaneous combination of the two elementary bodies that the flask containing them flies into pieces. The fact that this may also be brought on with a magnesium light which, as is the case with sunlight, is rich in chemical rays, indicates that we are dealing with a process in which heat plays a predominant part. Precisely as the sun sends radiations which the earth transforms into heat, so does it, in the experiment mentioned, send radiations which the combined chlorine and hydrogen transform into heat; the mixture absorbs the undulations of the ether and transforms

them into *molecular* energy, *i.e.*, heat. But a multitude of familiar every-day phenomena prove that increased molecular energy, or heat, may be procured without light-rays, etc.; the mere rubbing of a match against a dry surface will cause it to light, for instance. That this occurs without in the least involving the need of a chemical body on the substance against which the match is rubbed to start the reaction indicates that friction causes increased vibratory activity in the ingredients of the match-tip, and, these only combining when a given temperature is reached, *heat* must obviously be accepted as the causative factor of the process. Now, a very significant feature in connection with the formation of the gastric hydrochloric acid is the fact that *the combination temperature, when an immediate reaction is obtained between chlorine and hydrogen, is 39.5° C. (103.1° F.), while that of the gastric cavity is about 38° C. (100.4° F.).* The fact that the walls of the stomach, the seat of the blood-flow, must show a higher temperature than this (at least 2 degrees, that of the liver being 106 degrees) pointedly suggests that the formation of hydrochloric acid only occurs when the stomach is brought up to the required temperature.

Under these conditions, the formation of hydrochloric acid would be as follows: The volume of blood circulating in the gastric mucosa being increased by vasodilation of its arterioles under the auspices of the vagus, the oxidizing plasma, by enhancing metabolism, raises the temperature of the stomach at least the 1.5° C. required to render the formation of hydrochloric acid possible.

The acid would be formed when needed: a feature quite in accord with experimental data. The parietal cells of the glands, which are the seats of its formation, are only active during digestion, and then increase in size; they continue in this condition as long as the stomach contains food, and then return to their normal size. The following lines of Howell's also tend to indicate that my conception of the process may be the right one: "The chemistry of the production of free HCl also remains undetermined. No free acid occurs in the blood or the lymph, and it follows, therefore, that it is manufactured in the secreting cells. It is quite evident, too, that

the source of the acid is the neutral chlorides of the blood; these are in some way decomposed, the chlorine uniting with hydrogen to form HCl , which is turned out upon the free surface of the stomach, while the base remains behind and probably passes back into the blood."

Closely related with the formation of hydrochloric acid is that of pepsin. Landois,¹⁷ for example, writes: "The glands themselves contain no pepsin, but only a zymogen, namely, the pepsinogenic substance or propepsin, which occurs in the granules of the chief cells. The zymogen, of itself, exerts no influence upon proteids. If, however, it be treated with hydrochloric acid or sodium chloride, it is transformed into pepsin." The hydrochloric acid is formed by the parietal or oxyntic cells in the cardiac portion of the stomach, while pepsin is produced in the peptic cells which occur both in the cardiac and pyloric regions. The mutual influence of these products brings in other factors, however, which are reviewed at length in the second volume.

For the present, it may be said that my views as to the mode of action of the vagus and sympathetic nerves upon the cardiac arterioles elucidates several obscure points. Thus, the fact that the secretion of the gastric juice continues after division of the gastric nerves is explained by the passive dilation of the arterioles and the admission of an excess of arterial blood to the secreting elements. This leaves to the vagus alone the function of secretory nerve (in accord with Pawlow's teachings) since it is a vasodilator. The sympathetic has no function other than to restore the arterioles to their normal caliber after the digestive process ceases. On the whole, the functions of the stomach, in the light of my views, are carried on as follows:—

1. During the phase of gastric inactivity, the arterioles distributed to the mucosa and muscles of the stomach are constricted sufficiently under impulses received through their sympathetic nerves, to admit only sufficient blood into the secretory and muscular elements to insure their nutrition and the formation of the substances necessary for the digestive process, viz.,

¹⁷ Landois: "Text-book of Physiol.," tenth American edition, p. 293, 1905.

pepsinogen in the peptic cells, hydrochloric acid in the parietal cells and myosinogen in the muscular fibers.

2. *When digestion is to begin the arterioles are dilated by terminals of the vagus, and an excess of arterial blood being thus caused to circulate in the peptic, parietal, and muscular cells, gastric juice is formed and secreted, and muscular movements of the gastric walls are incited.*

3. *When the digestive process is to cease the arterioles are restored to their normal caliber by vasoconstrictor fibers of the sympathetic nerve, and the stomach resumes the passive state described in the first conclusion.*

4. *The oxidizing substance (adrenoxidase) which circulates with the blood-plasma in the cellular elements, secretory and muscular, sustains the functional activity of all these cellular elements, both during the resting stage and during digestion.*

INTESTINES.—The innervation of the intestines corresponds with that of the stomach. We find the same secreto-motor nerve the vagus, and, as constrictor of the arterioles, the sympathetic. Howell¹⁸ refers to the extrinsic nerves of the intestines as follows: "As in the case of the stomach, the small intestine and the greater part of the large receive visceromotor nerve-fibers from the vagi and the sympathetic chain. The former, according to most observers, when artificially stimulated cause movements of the intestines, and are, therefore, regarded as the motor fibers."

Among the earlier writers to observe that this applied both to the stomach and intestines were Remak,¹⁹ Weber, Pflüger, Budge and v. Braam Houckgeest, Ludwig and Kupffer,²⁰ and Englemann.²¹ This was confirmed by the more recent experiments of Bechterew and Mislawski.²² Jacobi,²³ Morat,²⁴ and Pohl.²⁵ Pincus and Panum both found that the intestinal movements persisted after section of both vagi, however, a feature which indicates that an inherent contractile power exists in the

¹⁸ Howell: "Amer. T. B. of Physiol.," p. 384.

¹⁹ Remak: Müller's Archiv, 1858.

²⁰ Ludwig and Kupffer: Zeit. f. ration. Med., Bd. II, S. 357, 1858.

²¹ Englemann: Archiv f. d. ges. Physiol., Bd. IV, 1871.

²² Bechterew and Mislawski: Archiv f. Physiol., Suppl. Band, S. 243, :

²³ Jacobi: Archiv f. exp. Pathol., Bd. XXIX, S. 171, 1891.

²⁴ Morat: Archives de physiol. norm. et pathol., T. V. p. 142, 1893.

²⁵ Pohl: Archiv f. exper. Pathol., Bd. XXXIV, S. 87, 1894.

intestines as well as in the stomach. Bunch,²⁶ Courtade and Guyon,²⁷ contend that contraction of the circular coat was never obtained by them by stimulating either nerve. But Cash²⁸ noted that waves of constriction passed down the intestine when substances were placed in it after the splanchnic nerves had been cut—evidence that the remaining nerve contained both sensory and motor fibers. Starling emphasizes this by the statement that “true peristaltic contraction is a coördinated reflex, carried out by the local nervous centers in the walls of the gut. He also points to various disturbing factors and to the means calculated to obviate them. “If these precautions are observed,” he writes, “stimulation of the vagus in the neck, after paralysis of the cardio-inhibitory fibers by means of atropin, will always produce an effect upon the intestinal movements.” Hallion and François-Franck²⁹ observing the same precautions, noted that stimulation of the peripheral end of the cut vagus caused marked vasodilation in the intestine. This proves the strictodilator properties of this nerve.

An inhibitory action of the vagus is also generally recognized. Pflüger, according to Bunch, “saw sometimes an increase, sometimes a diminution of the intestinal movements on vagus stimulation.” Bechterew and Mislawski concluded that while the vagus contained both motor and inhibitor nerves, the former predominated. Starling gives tracings in support of this view, and also states that “the vagus contains two sets of fibers to the muscular coat of the intestine,” one set inhibiting, the other augmentor or motor. Bunch also states that “the vagi contain both augmentor and inhibitory fibers for the muscular coat of the intestine.”

The sympathetic fulfills in this connection the same function that we found it to fulfill in other organs. “The fibers from the sympathetic chain, on the other hand,” as stated by Howell,³⁰ “give mainly an inhibitory effect when stimulated.” We have seen that this is due to an exaggerated contraction of

²⁶ Bunch: *Jour. of Physiol.*, vol. xxii, p. 25, 1898.

²⁷ Courtade and Guyon: *Archives de physiol. norm. et pathol.*, 1897.

²⁸ Cash: *Proceedings Roy. Soc. of London*, vol. xi, p. 469, 1886; vol. xii, p. 213, 1886.

²⁹ Hallion and François-Franck: *Archives de physiol. norm. et path.*, T. viii, p. 502, 1896.

³⁰ Howell: *T. B. of Physiol.*, second edition, p. 669, 1907.

the arterioles by the sympathetic terminals—proof that the latter act as vasoconstrictors. Briefly as elsewhere, function is incited by vasodilation, and arrested by vasoconstriction.

The kinship with the stomach applies also to the intestinal secretory organs. This is emphasized by the following lines of Piersol's: "The *blood-vessels* supplying the intestines follow the general arrangement of those of the stomach. The larger vessels pierce the serous and muscular coats, giving off slender twigs to supply the tissues of the tunics; upon reaching the submucosa the vessels form a wide-meshed net-work. Numerous branches then pass through the muscularis mucosa, to be distributed to the deeper as well as to the more superficial parts of the mucosa; narrow *capillaries* form net-works which *surround the tubular glands*, while beneath the epithelium wider capillaries encircle the mouths of the follicles. From this superficial capillary net-work the veins arise and, passing between the follicles, join the deeper venous plexus, which, in turn, empties into the larger vein of the submucosa. In those parts of the intestine where villi exist special additional arteries pass directly to the bases of the villi, when they expand into capillary net-works, which run beneath the epithelium and around the central lacteal as far as the ends of the villi. These capillaries terminate in venous stems, which descend almost perpendicularly into the mucosa, in their course receiving the superficial capillaries encircling the glandular ducts. Brunner's glands and the solitary and agminated follicles are supplied from the submucosa by vessels which terminate in capillary net-works distributed to the acini of the glands and to the interior of the lymph-follicles." . . . "The nerves distributed to the intestines are arranged almost identically to those of the stomach; they are composed largely of non-medullated fibers, derived from the trunks which pass within the mesentery from the *larger abdominal sympathetic plexuses*. After giving off branches to the serous coat, the nerves pierce the longitudinal muscular tunic to form the rich intramuscular plexus of Auerbach. This is composed of a rich net-work of delicate, pale fibers, at the nodal points of which microscopical ganglia exist; after supplying the longitudinal and outer part of the circular muscular coats the fibers obliquely pierce the

latter tunic to gain the submucous tissue, where they form the plexus of Meissner, which closely resembles Auerbach's nervous net-work within the muscularis, possessing, however, smaller ganglia and somewhat closed meshes. From the plexus of the submucous tunic fibers pass into the mucosa, to form net-works about the glands and to send fibrillæ into the villi."

In analyzing the functions of the intestinal tract it is important to note that two distinct sets of active structures are present: (1) the *secreting* glands of Lieberkühn and of Brunner; (2) the villi of the agminated lymph-follicles (Peyer's patches) and the solitary lymph-follicles.

Secreting Glands.—The glands, or crypts, of Lieberkühn, found in close array throughout the entire length of the intestine, including the colon, are present only in the upper, or mucous, layer. They are simple in construction and recall the sweat-glands, minus the coils and muscles: *i.e.*, a net-work of capillaries and probably nerve-fibrils overlying a delicate basement-membrane which in turn surrounds a single layer of columnar epithelial cells. These cells radiate toward a common center and thus form a minute tube which opens upon the mucous membrane between the villi. Their functional mechanism is doubtless that of all simple tubular glands.

Howell refers to the crypts of Lieberkühn as follows: "These structures resemble the gastric glands in general appearance, but not in the character of the epithelium. The epithelium lining the crypts is of two varieties: the goblet cells, whose function is to form mucus, and columnar cells with a characteristic striated border. . . . Whether or not the crypts form a definite secretion has been much debated. Physiologists are accustomed to speak of an intestinal juice, 'succus entericus,' as being formed by the glands of Lieberkühn; but practically nothing is known as to the mechanism of the secretion." We have seen that nerve-filaments are distributed to the secreting cells of the intestines, as stated by Piersol. The functional needs of these structures seem, therefore, to be satisfied. That they secrete mucus seems evident if their histological attributes can be taken as guide. As we pointed out in this work in 1903, however, the intestinal secretion serves also to protect the body against infection through foods.

INTESTINAL IMMUNIZING FUNCTIONS.—The gastric juice is not only concerned with digestion, but it is likewise a powerful antiseptic. Howell refers to this property in the following words: "One of the interesting facts about this secretion is the way in which it withstands putrefaction. It may be kept for a long time, for months even, without becoming putrid and with very little change, if any, in its digestive action or in its total acidity. This fact shows that the juice possesses antiseptic properties, and it is usually supposed that the presence of the free acid accounts for this quality." This might serve as evidence that beyond the pylorus further protection of this sort is unnecessary; but greater is the care with which Nature protects her organic creations. Every structural cell in any way exposed seems to be surrounded not only with prophylactic weapons, but also with second and even third lines of defense to cope with what the first line may have failed to disarm. Removal of the stomach in animals has been followed with return to normal health; it seems plausible that the intestinal tract should also be supplied with means for the protection of its organs.

The material formed in the living crypt of Lieberkühn first presents the form of granules, then becomes transformed into a transparent substance which accumulates in the spaces of the cell-substance. This either constitutes the mucin found in the secretion or represents an antecedent of this material. The secretion proper is clear, viscid, yellowish, and alkaline. That it may possess antiseptic properties is suggested by the fact that a very similar fluid,—*i.e.*, nasal "mucus,"—thanks to the labors of St. Clair Thomson and Hewlett,³¹ has been found to prove bactericidal. Page³² experimentally ascertained that nasal "mucus" killed anthrax bacilli, that Klebs-Löffler bacilli were almost actively destroyed by it, and that the virulence of staphylococci and streptococci was reduced. Nasal "mucus," however, is largely made up of serum: a feature which also applies to the secretion of the glands of Lieberkühn.

Brunner's glands, which occur in the duodenum, at the

³¹ St. Clair Thomson and Hewlett: *Medico-Chirurgical Transactions*, vol. lxxviii.

³² Paget: *Journal of Laryngology*, Nov., 1896.

portal of the intestinal canal, would seem to suggest, by their situation and their general conformation, just such a function. While they resemble in general structure the pyloric glands, to which most authors compare them, they also present many characteristics of the mammary lobules, especially in the manner in which their interlobular ducts are disposed. The gland proper is situated beneath the smaller crypts just described,—*i.e.*, in the submucous tissues,—its ducts penetrating to the surface between the villi or into the crypts of Lieberkühn: an indication that there is considerable analogy between their products. Indeed, their secretion is also serous: *i.e.*, blood-plasma relieved of its fibrin, globulins, etc.

The secretion of these two glands is termed “intestinal juice,” or “succus entericus,” and is regarded by many as capable of acting on starch, proteids, fats, etc., in connection with intestinal digestion: all properties which could not controvert any antiseptic power it might possess through the presence of oxidizing substance and alexins. Professor Foster, however, referring to this supposed action on foods, says: “Even at its best its actions are slow and feeble. Moreover, many observers have obtained negative results; so that the various statements are conflicting.” And he adds: “We may, therefore, conclude that at present, at all events, we have no satisfactory reasons for supposing that the actual digestion of food in the intestine is, to any great extent, aided by such a juice.” We will see in the second volume, however, that such is the case.

These two glands are the only ones forming part of the intestinal tissues *per se* to which the protective functions referred to could be ascribed. Hence, the facts that they both produce a secretion so nearly identical to blood-plasma as to be called “serous,”—for the glands of Lieberkühn are the source of serous diarrhœa, and the rice-water discharges of Asiatic cholera. Moreover, the recognized fact that blood-plasma is the normal excipient for chemical protective agencies, suggests, as a working proposition, that *the glands of Lieberkühn and the duodenal glands of Brunner supply a secretion having for its object to asepticize, and prevent the putrefaction of, the intestinal contents, besides taking part in the digestive process.*

The presence of a bactericidal fluid in the intestinal canal, at least along its walls, is suggested by various facts.

It is now generally recognized that the nursing infant receives through its mother certain substances which increase the bactericidal power of its blood-serum. Thus while Schmid and Pflanz³³ found experimentally that the antitoxic substances in the blood of parturient women exist also in the milk, Figari^{33a} also noted that calves and young goats are not only capable of absorbing agglutinins and antitoxins with the milk of immunized mothers, but that rabbits immunized by the administration of immunized milk taken by the mouth, are capable of transmitting to their young both agglutinins and antitoxins. This suggests that apart from the stomach general immunity may be conferred by fluids absorbed from the intestinal canal. This accounts for the fact that nursing babies are able to withstand more effectually than bottle babies both local and general infections. As will be shown elsewhere in this volume, the adrenal mechanism is not developed in the nursing sufficiently to protect the child against infection, and Nature insures, through the mother's milk, not only the child's nutrition, but its protection. Welch, in his Harvey Lecture, said: "It is an important function of the mother to transfer to the suckling through her milk immunizing bodies, and the infant's stomach has the capacity, which is afterward lost, of absorbing these substances in active state. The relative richness of the suckling's blood in protective antibodies, as contrasted with artificially-fed infant, explains the greater freedom of the former from infectious diseases."

The importance of this fact in practice, cannot be overestimated. "Among those who believe in the omnipotence of chemical formulæ," wrote Jacobi, recently, "there prevails the opinion that a baby deprived of mother's milk may just as readily be brought up on cows' milk; that is easily disproved. In Berlin they found that among the cows' milk-fed babies under a year, the mortality was six times as great as among breast-fed infants. Our own great cities gave us similar, or slightly smaller, proportions, until the excessive mortality of

³³ Schmid and Pflanz: *Wiener klin. Woch.*, No. 42, 1896.

^{33a} Figari: *Riforma Medica*, April 8, 1905.

the very young was somewhat reduced by the care bestowed on the milk introduced into both our palaces and tenements. Milk was examined for bacteria, cleanliness and chemical reaction. It was sterilized, Pasteurized, modified, cooled, but no cow's milk was ever under the laws of Nature changed into human milk; and with better milk than the City of New York ever had, its infant mortality was greater this summer (1904) than it has been in many years. That hundreds of thousands of the newly-born and small infants perish every year on account of the absence of their natural food, is a fact which is known and which should not exist." Winters states that "during the siege of Paris (1870-71), while the general mortality was doubled, that of infants was lowered 40 per cent. owing to mothers being driven to suckle their infants!"

This shows that the alimentary canal may be the seat of an immunizing process, and suggests that if the intestinal secretion of adult animals is bactericidal, the intestinal immunizing process must prevail at all ages. That the intestinal secretion are endowed with immunizing properties is suggested by various facts. Pawlow found that the succus entericus increased strikingly the proteolytic activity of the pancreatic ferments—sometimes to an astonishing degree. When we consider that Metchnikoff's "cytase," the substance which enables phagocytes to digest bacteria is mainly a pancreatic ferment, trypsin, it is self-evident that the same ferment should likewise digest bacteria in the intestine and thus protect the body at large. This is further suggested by the fact that Wender found that milk contained a ferment to which he refers as "galactase or trypsin," an observation confirmed by several investigators. The intestinal secretion can thus replace milk—obviously with greater activity—as an immunizing agent, since both fluids contain the same proteolytic and therefore bactericidal agents. We will see in the second volume that *all* the agents concerned in the immunizing process are present in the intestinal secretion as well as in milk.

That the bacteriolytic process occurs upon the surface of the intestinal mucous membrane is rendered probable by the fact that, as stated by Howell, "extracts of the walls of the small intestine or the juice squeezed from these walls have been

found to contain four or five different enzymes, and to exert a most important action upon intestinal digestion. Whether these enzymes are actually secreted into the lumen of the intestine," continues the author, "is not satisfactorily shown, but since they are contained in the intestinal wall, we must regard them as secretory products and consider them as the important and characteristic feature of the intestinal secretion."

The most direct evidence, however, is that furnished by Charrin and Levaditi, Zaremba, and others, who showed that the pancreatic juice could digest bacteria and their toxins. The investigations of Bordet, Metchnikoff, Ehrlich and Morgenroth having demonstrated that the distinction of bacteria in phagocytes was due to the presence in these cells of the corresponding pancreatic ferment, trypsin, it is difficult to conceive how, in accord with the prevailing views on the subject, intestinal bacteria, especially those ingested with foods, can escape digestion, along with the food-stuffs.

It is now believed that intestinal bacteria are necessary in the intestinal digestive process; but as Noel Paton (1905) states: "By taking embryo guinea-pigs at full time from the uterus and keeping them with aseptic precautions, it has been shown that the absence of micro-organisms from the intestine does not interfere with digestion."

For reasons that will be submitted in the second volume, the intestinal immunizing process is carried on mainly, as far as liquids are concerned, by a recently discovered ferment (a compound containing trypsin and the oxidizing substance, as I will show) which has been found to act more vigorously than trypsin, and termed "erepsin" by Cohnheim. It splits peptones and many other proteids into their component bodies, particularly the di-amido and non-amido acids leucin and tyrosin. It is thought to supplement the proteolysis begun by the trypsin. As bacteria are proteids, it follows that they are digested—and thus destroyed as living organisms—as well as the other proteids. Hence the intestinal immunizing process urged by myself in this work in 1903.

Pending additional testimony I may submit as a working proposition, the conclusion that *intestinal digestion of proteids includes that of living proteids, viz., bacteria and that this*

bacteriolysis represents a function through which general infection is prevented, i.e., an immunizing process.

Villi and Lymph-follicles.—The process of absorption, as now conceived by physiologists, is concisely described by Howell in the second edition of his text-book (p. 733): "Absorption takes place very readily in the small intestine. The general correctness of this statement may be shown by the use of isolated loops of the intestine. Salt solutions of varying strengths or even blood-serum nearly identical in composition with the animals' own blood, may be absorbed completely from these loops. Examination of the contents of the intestine in the duodenum and at the ileocecal valve shows that the products formed in digestion have largely disappeared in traversing this distance. All the information that we possess indicates, in fact, that the mucous membrane of the small intestine absorbs readily, and it is one of the problems of this part of physiology to explain the means by which this absorption is effected. Anatomically two paths are open to the products absorbed. They may enter the blood directly by passing into the capillaries of the villi, or they may enter the lacteals of the villi, pass into the lymph circulation and through the thoracic duct of the lymphatic system eventually reach the blood vascular system. The older physiologists assumed that absorption takes place exclusively through the central lacteals of the villi, and hence these vessels were described as absorbents. We now know that the digested and resynthesized fats are absorbed by way of the lacteals, but that the other products of digestion are absorbed mainly through the blood-vessels, and therefore enter the portal system and pass through the liver before reaching the general circulation. According to observations made upon a patient with a fistula at the end of the small intestine [Macfadyen, Nencki, and Sieber], food begins to pass into the large intestine in from two to five and a quarter hours after eating, and it requires from nine to twenty-three hours before the last of a meal has passed the ileocecal valve; this estimate includes, of course, the time in the stomach. During this passage absorption of the digested products takes place nearly completely. In the fistula case referred to above, it was found that 85 per cent. of the protein had disappeared, and similar facts are known regarding the other food-

stuffs." . . . "The energy that controls absorption resides, therefore, in the wall of the intestine, presumably in the epithelial cells, and constitutes a special form of imbibition which is not yet understood."

Various facts tend also to suggest that the intestine is the seat of a protective process, where bacteria and poisons of all kinds are most likely to penetrate the blood-stream: *i.e.*, the organs of the intestinal wall connected with absorption.

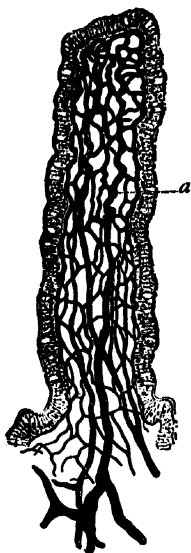
Viewed from my standpoint the question embodies features which seem to me to have been overlooked, but which require a review of the functions of each organ involved in the process studied, especially the villi and lymph-follicles. The villi, the solitary lymph-follicles, and the agminated lymph-follicles, or Peyer's patches, are considered together, because they appear to represent parts of a single system.

The structural similarity between the walls of the stomach and those of the intestine must be set aside here, since the function referred to,—*i.e.*, absorption,—a predominating one in connection with the intestines, can hardly be said to be worth considering as a factor of gastric functions. Conversely, the villi distributed throughout the whole small intestine are especially adapted for this purpose. Besides the capillaries, nerves, muscular tissue, basement membrane, and epithelium, these structures contain a lymph-trunk, or lacteal, the purpose of which is to take up nutritional agencies from the intestinal contents as they pass along.

Each villus may be considered as a sort of "reversed" gland, if a sweat-gland is taken as standard. The epithelium is outside—*i.e.*, exposed in the intestinal canal,—while under the epithelium lies the basement membrane. Combined, these two constitute a glove-finger-like projection inside of which are the structures that we found *over* the basement membrane in the sweat-gland. The capillaries form a close-meshed network not only in contact with the inside of the basement membrane, but entwined with considerable connective tissue strewn with leucocytes, the tissue and cells constituting "lymphoid tissues." I said "connective tissue," but at this point we must emphasize the fact that it is not *true* connective tissue, as met with elsewhere, but a fenestrated membrane made up entirely of star-like cells that give off thin projections, or

pseudopodia, which by intermixing make up the tissue itself: *i.e.*, Kölliker's *cytogenous tissue*. The fenestra, or openings, with which this cytogenous membrane is permeated accommodate the capillaries.

Another histological feature of special interest is the presence of smooth muscular fibers which stand upright—a few being horizontally disposed—and are interwoven among the capillaries and cell-fibers previously referred to. We thus have immediately under the villus's delicate basement membrane a



INTESTINAL VILLUS; VENOUS RADICLE SHOWN AT *a*. (*Cadiat.*)

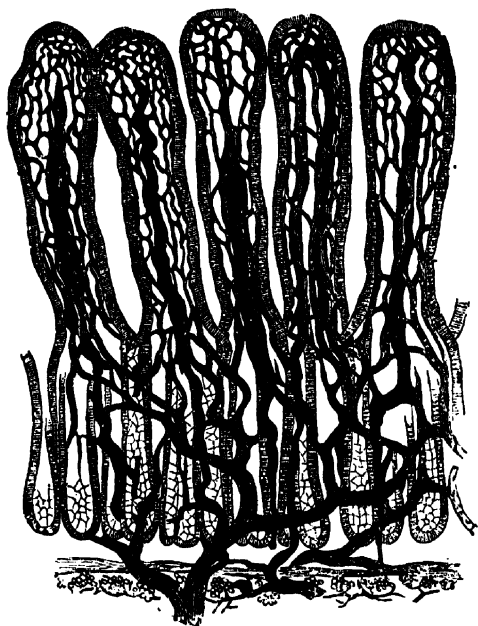
perfect, though minute, suction-pump which by alternately contracting and relaxing causes the organ to absorb the previously aseptized intestinal fluids.

Next in order inwardly are the venous stems (one or two) which carry the blood from the villous capillaries to the veins in the deeper tissues. These vascular channels, which carry the bulk of intestinal foodstuffs to veins which ultimately end in the portal system, are well shown in the annexed cut, and will again be referred to.

Last of all, in the middle of the organ, is the lacteal,—a

thick, club-like, sometimes double, lymphatic vessel, which stands upright and reaches almost to the inside of the tip of the villus, its own blind apex almost touching the former. Each lacteal represents the origin of a lymphatic vessel. This is illustrated in the second figure.

Lymph contains chyle—derived from the intestines—only during intestinal digestion. At other times the fluid found in the lacteal and neighboring structures is identical to that



INTESTINAL VILLI; INJECTED LACTEALS IN THE MIDDLE OF EACH VILLUS. (*Cadiat.*)

found elsewhere in the organism. It is perhaps advisable to emphasize the fact that lymph is very similar to blood-plasma, and richer than this fluid, owing to the presence of leucocytes. Indeed, it only differs from blood in the absence of red corpuscles. It undergoes coagulation and separates, as does plasma, into serum and clot, the latter likewise containing fibrin-globulins. It contains serum-globulin and serum-albumin in relative proportions similar to those in blood, though in smaller quantity: a feature which accounts for its somewhat

lower specific gravity. Inorganic salts, the chlorides preponderating, also correspond to those of the plasma. Being a vehicle for various substances, its constituents are variable quantities, and the conflicting analyses published are thus accounted for. Stewart says, in this connection: "Lymph has been defined as blood without its red corpuscles (Johannes Müller); it is, in fact, a dilute blood-plasma, containing leucocytes, some of which (lymphocytes) are common to lymph and blood, others (coarsely granular basophile cells) are absent from the blood. The reason for this similarity appears when it is recognized that the plasma of lymph is derived from the plasma of blood by a process of physiological filtration (or osmosis) through the walls of the capillaries into the lymph-spaces that everywhere occupy the interstices of areolar tissue. But, in addition to the constituents of the plasma, lymph appears to contain certain toxic substances produced in the metabolism of the tissues and destroyed in the lymphatic glands."

It now seems probable that the intestinal tract, being one of the two regions most exposed to toxics, the villi not only have for their function to absorb chyle, but to protect the organism. The lacteal is the recognized absorption organ for emulsified fats. As I view the process involved, the fat-containing fluids, as soon as they reach the basement membrane, are first submitted to the asepticizing influence of its endothelial cells. They are then submitted to the next process of epuration, and probably chemically transformed in the lymphoid layer—Kölliker's cytogenous layer—immediately beneath, in which leucocytes, and, therefore, antitoxic substances, are *constantly being formed*. When it finally reaches the lacteal, it again meets endothelial walls, and when through these and in the lacteal, must run the gauntlet of an accumulated array of fresh leucocytes from the cytogenous layer. The chyle, therefore, is met as soon as it enters the organism by all the latter's protective resources: phagocytes, stellate or connective-tissue cells, endothelial cells, and finally the oxidizing substance, the latter probably serving here to convert products of local metabolism and other toxic materials into inert bodies.

The villi, which thus absorb all nutrient substances assimilated by the organism whether by their venous stems or

their lacteals, are thickly distributed throughout the entire length of the small intestine. In the duodenum and jejunum they doubtless fully satisfy the needs of the organism, both as to absorption and prophylaxis. In the lower part of the intestinal canal, however, more protection is required, owing perhaps to continued exposure of the contents to a relatively high temperature during the time elapsed since this material has been submitted to powerful antiseptic treatment in the stomach: *i.e.*, several hours to a day, according to the meal. A morning movement of the bowels, for instance, includes products of the breakfast of the preceding day, thus representing twenty-four hours of exposure in the intestine to a temperature averaging 39° C. (102.2° F.). This additional precaution is represented by the solitary lymph-follicles and the agminated lymph-follicles, or Peyer's patches. While the solitary lymph-follicles are found throughout the entire canal, small and large, they are by far most numerous in the lower part of the ileum and in the first part of the colon. Peyer's patches, or the agminated follicles, are likewise found in the duodenum and jejunum, though rarely in the former; but their site of predilection is also in the ileum, and, inasmuch as they vary from one-half inch to four inches in length and are oval or round, they cover an extensive area, though only twenty to thirty in number. Especially is this the case since they are practically limited to one side of the intestine: *i.e.*, to the portion facing the latter's attachment to the mesentery. They also frequently form a continuous layer in the vermiform appendix.

A single "solitary follicle" is typical of them all, including those in Peyer's patches. A follicle consists, on the whole, of a rounded mass lodged in the submucous tissue, a small part of its upper portion appearing upon the free surface of the latter, though the epithelium of the intestine also covers it. The overlying layer of epithelium, however, is separated from the follicle by a special delicate membrane perforated with a multitude of holes that surround its projecting portion and communicate with the organ itself.

The structure of the body of the follicle will perhaps be best understood if it is divided into three different parts, be-

ginning from the inner portion of the organ. A fine network of capillary blood-vessels which acts as a supporting fabric, furnished by underlying arterioles, is the central feature; this, in turn, is surrounded with a close net-work of fibrils, in which "lymph-corpuscles, small round cells, with a large nucleus and very little perinuclear protoplasm" so completely preponderate as to almost entirely obscure the network.^{33b} But there is a feature of special interest here which will remind us of the cell-forming membrane of Kölliker found in villi: *i.e.*, a central nodule, described by Flemming, in which some cells undergo active karyokinetic division, while others, lymphocytes, are formed in continuous quantities. "In the center of the nodule," say Böhm and von Davidoff,^{33c} the cells often show numerous mitoses, and it is here that an active proliferation of the cells takes place. The cells may either remain in the lymph-follicle or the newly-formed cells are pushed to the periphery of the nodule and are then swept into the circulation by the slow lymph-current which circulates between the wide meshes of the reticular connective tissue." The third portion is the interval referred to, a delicately partitioned sinus which surrounds the follicle. To this sinus the lymph, originally from the blood-capillaries, after it has permeated the meshes and cell-spaces of the adenoid tissue and became charged with the newly created cells, gravitates, finally to find its way into the lymph-vessels of the submucous tissues beneath.

The physiological functions of the follicle seem plain when we consider two salient features of its anatomical relations with the mucous surface of the intestine and with the villi. As to the relationship between the interior of the follicle and the intestinal canal, it is suggested by the perforations to which we have previously referred, but there seems to be no mechanism to insure absorption. The case is not the same, however, in respect to the connection with the villi. Indeed, the lymphatic vessels which originate from the lacteals of the latter constitute the afferent supply of the sinus, while the lymphatic vessels of the submucous tissue represent its efferent system.

^{33b} Clarkson: "Histology," 1896.

^{33c} Böhm and von Davidoff: *Loc. cit.*

It is very evident, therefore, that we have, in each follicle, a powerful adjunct to the overlying villi, to add still another prophylactic means to those already enumerated. While the villi do not occur upon the portion of the follicle that projects into the intestinal free surface, they are nevertheless present *around* it, and their lacteals when below the level of the epithelium break up into vessels which find their way to the lymph-sinus. "When they reach the level of the closed follicles," says Berdal,^{33a} "the chyloferous vessels become united to the sinuses of these follicles, of which they constitute the afferent vessels. Crossing the muscularis mucosæ, they form part of a varicose capillary net-work in the submucosa. From this net-work arise true lymphatic trunks supplied with valves that cross the intestinal coats and then reach the subperitoneal lymphatic net-work."

The intimate relationships between the villus and the lymphatic follicle is further emphasized by the similarity which their mechanisms present. If the lymph-sinus of the latter is considered as functionally encircling what in the villus has been termed *cytogenous tissue* by Kölliker, including its network of capillaries, this similarity becomes striking. Indeed, the fact that the sinus is situated around the lymphoid tissue instead of in its center, as it is in the villus, would tend to indicate that the follicle does not absorb intestinal fluids, since these would merely, before reaching the sinus, be subjected to what epuration the epithelium and the fenestrated membrane overlying the organ could afford. It is, therefore, probable that the solitary follicle or organ does not include absorption among its attributes. Indeed, unless possessed of a suction mechanism such as that of the villi, it is evident that, surrounded, as is its projecting part, by these minute pumps, its usefulness would be very slight.

What can be the use, therefore, of the minute apertures encircling the projecting part of the follicle and which constitute the "fenestrated" subepithelial membrane? "These orifices appear," says Berdal, "to afford passage to lymphatic cells that emigrate from the follicle toward the cavity of the

^{33a} Berdal: "Histologie Normale," p. 365, 1894.

intestine,"—and to assist, if considered from my standpoint *in asepticing the contents of the lower end of the small intestine by permeating it with mobile phagocytes and alexocytes*. If we now connect this fact with the predilection of Peyer's patches for bacterial invasion in typhoid fever, it would seem as if functional impairment of these organs would render possible the pullulation of pathogenic organisms in the ileum. This would normally lead to infection of the patches, and of the system at large through the apertures.

Besides this first, and I may add, very important protective function, the follicular sinus, by serving as a secondary passage for the chyle, appears to afford a supplemental protection to the organism of no mean power when we consider that it serves not only as a channel for freshly-manufactured leucocytes, but that the follicle simultaneously receives freshly-oxidized blood directly from the great arterial trunks, through the mesenteric arteries. This blood, which reaches the lymphoid tissue through the rich intrinsic capillary net-work to which I have referred, doubtless furnishes it with the various elements required for the metamorphoses—retrogressive and progressive—noted by Flemming and others, then forces its way into the sinus, carrying with it not only the newly-created cells, but also serum supplied with all the defensive agencies which the blood affords. The accumulation of Peyer's patches in the lower two-thirds of the ileum seems to point directly to this as the most toxic part of the canal—and clinicians well know how frequently this region becomes the seat of intestinal disease.

It would thus appear as if in the duodenum, the jejunum, and the upper part of the ileum, the gastric juice, the secretion of the crypts of Lieberkühn and that of the glands of Brunner, in addition to the ultravillous process, would subserve the protective process; and that beyond this, to the end of the ileum, the follicles, either solitary or agminated in patches, the villous process *plus* the folliculous process, including the output of lymphocytes into the intestine, united to accomplish the same prophylactic purpose.

The colon is deprived of villi, but plentifully supplied with crypts of Lieberkühn, while solitary glands, somewhat larger

than those in the ileum, are scattered throughout its entire extent. The former doubtless furnish the mucus, while the latter probably contribute the asepticizing lymphocytes.

Here as in other organs of the alimentary system the sympathetic system alone, through its vasoconstrictors, does not account for the phenomenon which initiates function, *i.e.*, vasodilation. This is supplied, as in the stomach, by the vagus.

Disturbance of the functions of the adrenal system by lesions of their nerves seriously hampers the intestinal immunizing process. Onuf and Collins refer as follows to the disturbances that result from extirpation of the stellate ganglion in cats: "They consisted of diarrhoea and putrefaction of the faeces. The faecal matter was semiconsistent, of yellow or dark-grayish-brown color, and of exceedingly foul odor. This putrefaction of the faeces was observed in two of the three animals from which we removed the stellate ganglion. In the third cat they were not noted; but it should be added that this cat was killed before a time corresponding to that which had elapsed antecedent to the occurrence of putrefaction in the first two cats. The putrefactive symptoms made their appearance as late as two or three months after the operation, and it was noted that the digestive disturbances had a tendency to increase and persisted until the death of the animals, three and four and one-half months, respectively, after the operation. In one instance the autopsy revealed marked anamia of the intestines."

We are dealing, in these experiments, less with the effects of section of intestinal nervous supply on the local vascular walls than with those of impaired adrenal functions, as the extirpated stellate ganglion contains fibers to the thyroid, whose secretion sustains the functional activity of the adrenal center. Decrease of adrenal secretion, *i.e.*, of oxidizing substance in the plasma, was the main morbid factor. The functional energy of the intestinal crypts, glands, and follicles being impaired through loss of part of their *pabulum energeticum* in the blood, the asepticizing secretion of the crypts of Lieberkühn and the glands of Brunner became reduced, the production of lymphocytes by the follicles likewise, while the reduction of oxidizing substance in the secretions *per se* contributed to fur-

ther impair their prophylactic qualities. Onuf and Collins also refer to one of their animals operated in the same way, in which diarrhœa developed in two weeks; the third week "the animal began to be uncertain in gait, which increased to well-marked staggering" . . . "within two days it died in collapse." That the functions of important organs—the thyroid and adrenals—had been impaired, is evident.

The following deductions seem to me to be warranted by the analysis submitted:—

The glands of Lieberkühn and the duodenal glands of Brunner supply a secretion the purpose of which is to asepticize the intestinal contents.

The villi, through their venules and lacteals, absorb nutrient and chyle-forming materials from the intestinal foodstuffs, and the contents of the lacteals are submitted to a further asepticizing process, mainly in Kölliker's cytogenic membrane.

The solitary and agminated lymph-follicles (Peyer's patches) are cytogenic structures which further asepticize the materials absorbed by the surrounding villi, the efferent lymph-vessels of the latter constituting the afferent lymph-vessels of the follicles, where both kinds of organs occur together: i.e., in the portion of the small intestine in which pullulation of pathogenic bacteria is most likely to occur, the ileum particularly.

The solitary and agminated lymph-follicles also supply leucocytes to the intestinal canal, which leucocytes are formed in their cytogenic area (Flemming's central nodule) and pass out through the fenestrated membrane overlying each follicle. The purpose of some of these leucocytes is to insure the destruction of pathogenic agents formed as a result of putrefaction of the intestinal contents or introduced into the intestine.

In the colon, the asepticizing process is fulfilled by a rich supply (1) of Lieberkühn's crypts, which keep its walls bathed with their muco-serous secretions; and (2) of irregularly scattered solitary lymph-follicles, which supply the latter secretion with bactericidal cells and their antitoxic blood-serum.

The nervous supply of the intestines is derived from the vagal and sympathetic systems, the distribution to the various intestinal coats and their mode of action being similar to that of the same nerves in the stomach: While the vagal fibers ini-

tiate function by causing vasodilation, the sympathetic fibers arrest function by restoring the arteries to their normal caliber.

VERMIFORM APPENDIX.—Solitary follicles being also very numerous in the cæcum, and the appendix so rich in agminated follicles as to have suggested to some anatomists that it was a large Peyer's patch, I was led, in view of the facts presented in the foregoing pages, to the conclusion that:—

The cæcum, being particularly exposed to the accumulation of putrefactive materials, is supplied with an organ in which agminated lymph-follicles are particularly numerous, i.e., the vermiform appendix. The functions of this organ, therefore, appear to be to supply the cæcum with bactericidal cells and their products, i.e., phagocytic leucocytes and alexocytes (in addition to those supplied by the caecal agminated follicles) and antitoxic blood-serum.

Shortly after this conclusion had been published in the first edition of the present work (January, 1903, page 323) Prof. McAdam Eccles, of London,^{33e} stated, in his Hunterian Lectures, that practically little or nothing was known concerning the functions of the appendix, though he thought that it was probably "in part absorptive and in part excretive." Favoring the latter view he pointed out that the action of the muscular fibers in its muscular coat tended "to force its contents toward and into the cavity of the cæcum," the caliber of the aperture, "while amply sufficient in its natural state to allow the free evacuation of secretion from the mucous membrane of the tube itself." He also shows that in at least two of the fairly common positions of the organ, its orifice was so situated as to facilitate "the exit of the secretion." Corpe^{33f} in experiments on dogs found that the appendix secreted considerable fluid, estimating this at four ounces daily in these animals, and that the secretion was powerfully germicidal. Hoefer^{33g} noted, in the course of appendicectomy, that the appendix secreted a light, straw-colored fluid, and refers to Macewen as having seen a stream of alkaline fluid poured from the appendix just before the caecal contents passed into the colon. Each time a small quantity of chyme passed the orifice of the appendix it would become

^{33e} Eccles: London Lancet, March 14, 1903.

^{33f} Corpe: Medical Sentinel, May, 1903.

^{33g} Hoefer: St. Paul Med. Jour., Jan., 1907.

smearcd by the exudation therefrom. Condl is referred to as stating that six ounces of this fluid were secreted in the twenty-four hours. Hoefcr concludes with Bunge and others that the purpose of this fluid is to alkalize the cæcal contents before its migration to the colon. Recently, however, E. M. Corner, of London,^{33h} after a comprehensive study of the subject, concluded that the vermiform appendix was "a specialized part of the alimentary canal, nature having made use of a disappearing structure and endowed it with a secondary function, by giving it lymphoid tissue to protect the body against the micro-organisms of the ileo-cæcal region." The trend of evidence, therefore, is toward the immunizing function I attribute to the organ, a rôle which the resemblance of the glandular elements of the appendix to the tonsils had led various observers, notably Kilbourn,³³ⁱ to suspect.

THE LIVER AND ITS PHYSICO-CHEMICAL FUNCTIONS.— There is considerable evidence available to show that oxidation is one of the most active factors of hepatic functions, and yet it must be admitted that, according to prevailing views, there is no blood-supply capable of accounting for this powerful source of energy. To the portal vein, essentially a channel for physiologically impotent blood,—i.e., blood replete with the waste-products of four important organs and the oxygen of which has been utilized in these organs,—is ascribed this preponderating rôle. On the other hand, the hepatic artery is thought to supply the liver "with the blood of nutrition." Text-books on physiology, therefore, seldom refer to this vessel; works on histology hardly grant it more than two or three lines, if they refer to it at all. In text-books on anatomy it receives more attention, but only in its general topographical bearing.

As viewed from my standpoint, *the hepatic artery does not only supply the liver with its nutritional blood, but simultaneously with the blood upon which all its functions depend.*

To develop this proposition a review of the histology of the lobule is necessary. Clarkson³⁴ gives the following complete, though succinct, description of this wonderful little body

^{33h} Corner: *Annals of Surgery*, Oct., 1910.

³³ⁱ Kilbourn: *Philadelphia Med. Jour.*, May 17, 1902.

³⁴ Clarkson: "Text-book of Histology," 1896.

—about one-twentieth of an inch in diameter—and which in itself has been termed a “miniature liver”:—

“A lobule of the liver is polygonal in shape, and is composed chiefly of a number of gland-tubes, which radiate from near the center of the lobule to the periphery, where they open into their ducts. Thus, the blind terminal end of the tube is turned toward the center of the lobule; the ducts at the periphery lie in the interlobular connective tissue, which to the naked eye marks the boundaries of the lobule.

“The blood brought to the liver by the *portal vein*³⁵ is conveyed along its subdividing branches till the ultimate subdivisions are reached, which lie, together with the bile, in the connective tissue surrounding the lobules. Here capillaries are given off which pierce the lobule and pass between the radiating gland-tubes to reach the center, where they open into the intralobular radicle of the efferent vein of the liver, the *hepatic vein*. These small hepatic radicles open into the larger vessel,—the *sublobular vein*,—and the sublobular veins unite to contribute to the hepatic vein itself. The walls of the branches of the hepatic vein are destitute of muscular fibers and the adventitia is extremely thin. The radiating gland-tubes anastomose laterally with each other, as do the capillaries also. The meshes of the net-works are elongated in a radial direction. Thus, a lobule is composed of a radiating system of gland-tubes and a corresponding radiating system of capillaries lying between them. A very minute quantity of connective tissue accompanies the capillaries as an adventitia and in this lymphatic channels are to be found separating the gland-tubule from the blood-vessel.

“The lobule is surrounded (in part or whole) with connective tissue supporting branches of the afferent portal vein,—the feeder of the capillary net-work,—and the *bile-ducts*, which receive the secretion of the gland-tubules. Thus, the blood flows from the periphery to the center of the lobule; the bile, from the center to the periphery.

“But in addition to the afferent portal vein and the bile-ducts another vessel is found in the interlobular connective

³⁵ The italics are my own.

tissue. This is the *hepatic artery*, which supplies blood for the nutrition of the connective tissue of the organ, the vessel-walls, etc. It ultimately terminates in the small portal veins, and perhaps partly in the capillaries in the periphery of the lobules."

There exists some uncertainty as to the manner in which the subdivisions of the hepatic artery are related to the other perilobular and intralobular vessels. Pick and Howden³⁶ refer to its terminal distribution as follows: "Finally, it gives off interlobular branches, which form a plexus on the outer side of each lobule, to supply its wall and the accompanying bile-ducts. From this lobular branches *enter the lobule* and end in the capillary net-work between the cells. Some anatomists, however, doubt whether it transmits any blood directly to the capillary net-work." Harrison Allen³⁷ says: "Each lobule is a miniature liver having at its periphery between the lobules branches of the portal vein and hepatic artery (interlobular branches) which freely *intercommunicate* and form *through the lobule*, between its periphery and center, a capillary net-work. Directly at the center the venules of this net-work (intralobular vessels) converge to form radicles of the hepatic vein." Labadie-Lagrave³⁸ states that, "as regards the divisions (of the hepatic artery) destined for the lobules, they penetrate conjointly with interlobular veins, *but without communicating* with them, in the interior of the lobule, in the form of capillaries distributed to the *central vein*." In the presence of these divergent views, which but exemplify those of other authors, our only choice lies in the selection of the one region which all authors seem to consider as reached by the artery: *i.e.*, the periphery of the lobule. But, as all concede, also, that the arterial capillaries penetrate in one way or another to the intralobular supply, we will adopt—though we believe that Harrison Allen's definition is the true one—the more conservative distribution indicated in the annexed engraving by Piersol, who, in accord with many histologists, describes the

³⁶ Pick and Howden: "Gray's Anatomy"; edition, 1901.

³⁷ Harrison Allen: "Human Anatomy," 1884.

³⁸ Labadie-Lagrave: "Traité des Maladies du Foie," 1892.

hepatic' artery as "supplying nutrition to the interlobular structures and terminating in the lobular capillary net-work."

A noteworthy feature of the capillary net-work enveloping the cellular bodies is that each mesh does not merely cover one cell, but several. Indeed, were it otherwise, the bile-capillaries could not exist as individual channels and give an uninterrupted free way to their contents without allowing the bile to penetrate the blood-stream. To prevent this, and yet simultaneously insure perfect exposure to the blood and lymph, a very simple arrangement exists: *i.e.*, three or more of the



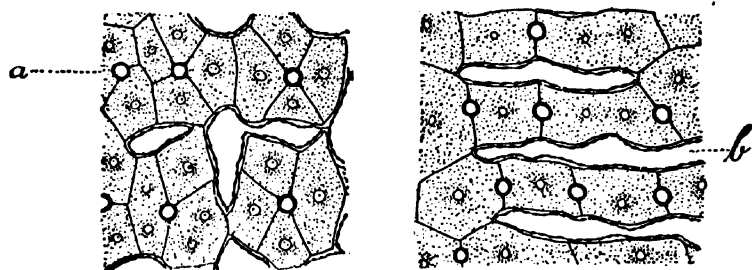
SECTION OF LIVER SHOWING THE LOBULES, CELLS, AND THE BLOOD-SUPPLY. (*Piersol.*)

P.V., Portal vein. H.A., Hepatic artery. H.V., Hepatic vein.

cells (usually polyhedral) are joined longitudinally, and, while the narrow passage in the center of the group thus formed serves as a bile-channel, the outside only is in contact with the blood- and lymph- capillaries. When only two cells are thus joined, the surfaces in contact have in their center a small opening, which, being adjusted to that of the adjoining cell, insures the continuity of the channel. It thus becomes clear that the blood-plasma may penetrate the cell, undergo or induce metabolism therein, and the product pass out through the intercellular biliary passages or bile-capillaries. The cells

are so joined as to form continuous, though correlated, channels, which radiate from the center of the lobule to its periphery, where they join the interlobular bile-channels.

The intimate structure of the hepatic cell is peculiar. It possesses no limiting membrane; but its peripheral protoplasm is more dense than that of its other parts and the pseudocovering so formed serves as the outer wall for numerous cavities or vacuoles which inosculate irregularly throughout its interior. All these vacuoles, however, more or less directly converge toward the center, where they meet a protoplasmic mass, which in turn contains one and sometimes two nuclei. The cell, apart from its nucleus, suggests a miniature sponge the cavities of which (secretion vacuoles) become filled with



BILIARY CANALICULI. (Mathias Dural.)

a, A biliary canaliculus cut transversely. *b*, Intercellular capillary.

glycogen. This substance seems to accumulate in the *outer* vacuoles, which appear wider in this location than the inner ones, when, by artificial means, the glycogen has been removed. It is perhaps noteworthy that this substance accumulates in the part of the cell nearest the blood-vessels and that the droplets, or "granules," considered as bile are most abundant in the opposite direction: *i.e.*, near the bile-capillaries. These "droplets" accumulate between periods of digestion and diminish during this process. A delicate canaliculus connects this part of the cell with the biliary channel. The vacuoles in the paraplasm, according to Kupffer, "play an important part in the secretion of the cell, and are due to the confluence of minute drops of bile into a large globule. As soon as the vacuole has attained a certain size it tends to empty its con-

tents into the bile-capillary through a small tubule connecting the vacuole with the bile-capillary." Kupffer's main vacuole is thought by him to constitute an intracellular vesicle connected with the bile-capillaries by means of delicate tubes.

The nerves of the liver enter the organ at the transverse fissure and accompany the blood-vessels and lymph-vessels to the interlobular spaces. That the vagus causes vasodilation of the hepatic arterioles was first observed by Cavazzani and Manca.³⁹ François-Franck and Hallion⁴⁰ also witnessed vasodilator effects on stimulating the central segment of the divided vagus with a weak current. Bruno⁴¹ has shown, moreover, that the flow of bile was increased concomitantly with the passage of food-products through the pylorus under the influence of the vagus.

The vasoconstrictor action of the sympathetic nerve on the liver was pointed out by Vulpian⁴² who found that stimulation of nerves derived from the celiac plexus caused anemia of the hepatic area to which they were distributed. Haffter, Samuel and Frenichs all observed congestive coloration phenomena on dividing the splanchnic nerve and the celiac plexus, similar to those that follow, in the ear, face, etc., section of the sympathetic nerve in the neck. Mall⁴³ showed that the splanchnics also contained vasomotor fibers for the portal vein. Bayliss and Starling⁴⁴ then found a rise of the blood-pressure in the portal vein occurred in the dog, when the thoracic nerves between the third and eleventh thoracic inclusive were stimulated, the maximum effect following excitation of the fifth to the ninth inclusive. Cavazzani and Manca⁴⁵ were led to conclude that hepatic vessels were also under the influence of such nerves by passing warm saline solution at a given pressure through these vessels and measuring the outflow in a given time. This was confirmed by François-Franck and Hallion.⁴⁶ The latter physiologists showed, moreover, that the

³⁹ Cavazzani and Manca: *Archives ital. de biol.*, T. xxiv, p. 33, 1895.

⁴⁰ François-Franck and Hallion: *Arch. de physiol. norm. et path.*, T. viii, and ix, 1896.

⁴¹ Bruno: *Archives des Sc. biol.*, T. vii, p. 87, 1899.

⁴² Vulpian: *C. R. de la Soc. de biol.*, p. 5, 1858.

⁴³ Mall: *Archiv f. Physiol.*, S. 409, 1892.

⁴⁴ Bayliss and Starling: *Jour. of Physiol.*, vol. xvii, p. 120, 1894.

⁴⁵ Cavazzani and Manca: *Loc. cit.*

⁴⁶ François-Franck and Hallion: *Loc. cit.*

true vasoconstrictor effects of the sympathetic were produced by fibers derived from the cord on a level with the sixth thoracic and second lumbar inclusive, all passing to the splanchnic nerves.

On the whole, it is evident that *the functions of the liver are incited through vagal vasodilators and inhibited by sympathetic vasoconstrictors as in the stomach and intestines.*

Our inquiry into the character and composition of the substances that are transformed in the liver and of the secretions of this organ must necessarily include the blood of the portal vein, since it contains whatever products of metabolism the organ is thought to transform. We shall, therefore, begin with this channel, which brings to the liver essentially venous blood, since it contains that utilized by four organs—the stomach and the intestines, the pancreas and the spleen—in which the metabolic products include, besides those incident upon tissue-waste, food metabolites, physiological toxics, etc.

As is well known, there exist in the liver's secretions distinct evidences of association with splenic hamatopoietic or hæmolytic functions. The liver is known to modify the composition of the blood as it passes through it, but the purposes of the alterations involved are not established.

The Splenic Vein.—The path from the spleen to the portal vein, through the splenic vein, is a direct one, and the blood the spleen sends to the liver is not, therefore, modified in transit by any other organ, though the splenic vein receives a few branches from the pancreas and stomach. Still, these are mere tributaries to a common channel, and, as the arterial supply comes directly from the celiac plexus, we can say that the spleen receives nothing but pure, freshly-oxygenated blood in great quantities. Indeed, the splenic artery is remarkably large for the dimensions of the organ, and *we can easily account for the so-called "ague-cake" and the temporary enlargement that occurs during malarial and other fevers when we include suprarenal overactivity and excessive vascular tension in the pathogenesis of these phenomena.*

To this we cannot ascribe, however, the post-prandial splenic enlargement, which attains its maximum about five hours after an ordinary meal, since we now know how inde-

pendently of suprarenal overactivity and merely through nervous influence an organ's function can be excited and governed; indeed, sympathetic and pneumogastric again unite here to account for a *passive* period and for an *active* period: that of gradual enlargement. "The turgescence of the spleen seems to be due to a relaxation both of the arteries and of the muscular tissue of the capsule and of the trabeculae" says Professor Foster: evidence that we are again dealing with dilation of the arterioles to increase the influx of blood into the functional areas,—the physiological process we have found in other organs.

That the organ is concerned with some process incident upon blood-changes is evident. But what is this process? The various points that may afford a clue are these: red blood-corpuscles have been found in various stages of disorganization in the organ, but in the interior of amœboid cells buried in the pulp. The spleen-pulp also contains an albuminoid proteid rich in iron, and a pigment which shows considerable carbon. That an active combustion process may go on in the organ is suggested not only by the latter, but also by the presence of various purin bases; xanthin, hypoxanthin, and their end-product, uric acid. Various other acids—acetic, butyric, formic, succinic, lactic, etc.—are also found in relatively large quantities. This appears suggestive when we consider the large quantity of oxidizing substance that must course through the organ especially during post-prandial activity.

The spleen also seems to be a leucocyto-genic center, since the splenic vein contains a much larger proportion of leucocytes than the splenic artery. But as these leucocytes leave the organ through the splenic vein, and ultimately, therefore, reach the liver through the portal, they must either be connected with some function in the liver or be destroyed there. Again, the arterial blood has been found to lose one-half of its red corpuscles; at least, blood from the spleen contains one-half of those found in the blood of the splenic arteries. Coupled with the finding of disorganized remnants of these bodies in the splenic pulp, this certainly suggests, as is generally believed, that red blood-disks are disintegrated and white corpuscles created in the spleen. Indeed, the portal blood is poor in red disks. Yet, the hepatic vein is still poorer in them

in the sense that the proportion of red to white cells is as four in the subhepatic vein is to one in the portal vein, after the blood has been submitted to the effects of hepatic functions. It seems clear, therefore, that red corpuscles are destroyed both in the spleen and in the liver, and that, since the spleen is possessed of no external duct, it is in the liver's secretions that we should find proofs of this dissociation of corpuscular elements. Indeed, we have in bilirubin, a bile-pigment derived from hæmoglobin, direct evidence of this fact.

The Hepatic Blood-pigments.—We have already analyzed (in the second chapter) the process through which various blood-pigments are transformed one into another. We will now only refer, therefore, to the relations between these bodies and the spleno-hepatic functions.

We ascertained that the changes undergone in the liver represented but a portion of a cycle of which the intestines were the starting-point, bilirubin (excepting that transformed into urobilin and stercorin) being reabsorbed from the intestine and again used in the building up of hæmoglobin. Experimental evidence was adduced to show (Macallum) that in an animal fed on albuminate of iron free leucocytes crowded with iron-pigment could be traced in transit through the intestinal mucous membrane in the villi, and that similar leucocytes had been found in the spleen and in the liver. But can we conclude from this that the iron-laden leucocytes find their way to the spleen and that this organ constitutes a part of the cycle? The anatomical relations of the structures involved show that, even if such an arrangement did exist, it could serve no useful purpose, since the leucocytes would but penetrate the splenic structures to again enter the portal circulation. Obviously, the only pathway available anatomically is the venous one, since Macallum found the "leucocytes crowded with granules of iron-pigments" in the *venules* of the villi.

The single venous channel at our disposal, therefore, is that of the distribution of the villi, the ileum and jejunum mainly, *i.e.*, the superior mesenteric veins,—which again lead us to the portal vein. This probably means that the iron thus taken from the intestine is not ready for the circulation, and

that it must undergo a secondary process in the liver before it can serve its physiological purpose in the arterial circulation. This is sustained by the prevailing view as to the functions of the spleen, *i.e.*, that it disintegrates worn-out red corpuscles, and also by the great increase of leucocytes observed in the splenic vein as compared to the proportion of these cells in the artery. It seems logical, therefore, to conclude that *both in the lymphatic structures of the intestine and in those of the spleen leucocytes are formed which carry iron-pigments to the portal vein; those from the intestine reach the latter by the superior mesenteric vein, and those from the spleen by the splenic vein.* As Macallum observed iron-pigment leucocytes in the spleen similar to those witnessed in the intestinal villi, and the venules of the latter and the splenic vein ultimately transmitting their blood to the portal vein, no other conclusion seems possible.

The similarity of the general mechanism involved suggests the presence of correlated functions. Thus, *in the spleen the leucocytes are formed in situ, pass out into the pulp-channels, and take up the iron-pigment and carry it out to the liver; in the intestine they are formed in a similar structure,—the follicle,—pass out into the intestinal channel, take on a similar supply of blood-pigment, re-enter through the villi into the venous system, and also proceed to the liver.* True, I have previously ascribed bactericidal properties to the leucocytes produced by the intestinal follicles; but the chemotactic property of the leucocytes, the existence of which is shown by their ability to take up the pigments, serves but to demonstrate that they must also be endowed at least with phagocytic attributes.

It was also shown, in the earlier editions of this work, that, while the adrenals supply an oxidizing substance to the blood, insufficiency of the adrenals leads to the formation of a compound inferior to hæmoglobin in oxygen-absorbing powers,—*i.e.*, methæmoglobin; and, furthermore, that hæmatoporphyrin is formed when the suprarenal insufficiency is still further advanced, hæmoglobin being unable to hold itself together, as it were, and to absorb oxygen. Again, we saw that hæmoglobin is reduced to hæmatin when the reaction with the reducing agent occurs in the *presence* of oxygen. In the *absence* of oxygen

a hæmochromogen is formed which slowly loses its iron, the end-product being also hæmatoporphyrin.

It is evident that the integrity of the hæmoglobin molecule is dependent upon the quantity of secretion that the adrenals supply to the blood, and also upon the condition of that molecule at a given time. In other words, while the adrenals may be supplying their normal proportion of secretion, the hæmoglobin molecule in the red corpuscles of venous blood—i.e., blood about to return to the vena cava for a fresh supply—may be compared to that of blood during insufficiency. Even as hamoglobin, the blood-pigment is loosely combined; when approaching the end of its systemic circle, it is still nearer the state of disintegration—according to the activity of the oxidation processes which it has subserved. Starting from the lungs as oxyhæmoglobin, it returns promptly to the heart as hæmoglobin or reduced hæmoglobin, ready to absorb at once another supply of suprarenal secretion and, once in the lungs, take up its oxygen.

Blood from the head, extremities, and other structures in which the drain upon its resources has not been excessive returns such a molecule to the heart; it is still efficient as an oxygen-carrier. *But not so with the blood from any organ directly connected with the digestive system.* As is well known, all the blood from the organs of the alimentary tract—stomach, intestine, pancreas, and spleen—is not returned to the heart before it has been submitted to whatever action the liver may have upon it; then only can it re-enter the circulation through the hepatic veins, which carry the blood to the vena cava. But not all the blood may thus be rejuvenated; some has gone beyond; it has, indeed, almost reached the state of hæmatoporphyrin, the last on the list of pigments, that which appears in the most advanced stages of suprarenal insufficiency. We have seen that hæmatoporphyrin and bilirubin are similar; and, as is well known, it is bilirubin which passes out with the bile.

A salient feature of the hæmoglobin molecule is missing here, however, namely: the iron. As stated, a reducing agent, if used in the presence of oxygen, will reduce hæmoglobin in the absence of oxygen; the primary product is a hæmochromogen which gradually parts with its iron, leaving as end-

product hæmatoporphyrin. As bilirubin and hæmatoporphyrin are fundamentally identical, the presence of the former in the bile must be the result of a similar process in the liver. That such is the case is sustained by considerable collateral evidence, first of which is the invulnerability of the hæmoglobin molecule.

Paradoxical as this statement appears, it nevertheless constitutes the key-stone of the entire edifice, since it is only when *vulnerable* that the molecule becomes the prey of disintegrating influences. I have used the words "reducing agents" several times; but the hæmoglobin molecule does not yield to even moderately-strong reagents of this nature; indeed, only a powerful agent—sulphuric acid, for instance—will dissociate it: an exemplification of the wonderful binding power which the suprarenal secretion must exert upon all its constituent parts. Still, we must not overlook the fact that the oxidizing substance in the blood-plasma is identical to this binding compound. Indeed, I have accumulated so much testimony affirming the fact that the plasma *per se* is a potent source of energy, while the red corpuscles always played so secondary a rôle in the various intrinsic functional mechanisms, especially those concerned with muscular and glandular elements, that I have been led to conclude that the red disks are, after all, but servants of the blood-plasma: pack-mules, as it were, from which it can draw, as needed, enough oxidizing substance to maintain its own functional potentiality as previously stated.

Under these circumstances we can readily see how the hæmoglobin molecule, gradually deprived of its binding oxidizing substance during the inordinate metabolism which the tissues of the digestive organs undergo during their periods of activity, should yield more readily to dissociating influences. It is evident that a molecule so weakened, thrust in blood such as that of the portal vein,—a vast sewer replete with physiological waste-products and deoxidized blood-cells, all bathing in a plasma itself despoiled of its oxidizing substance,—should soon become dissociated. Transported through gradually narrowing channels, the walls of which, like all tissues, eagerly absorb any loose oxygen that it may contain, it must inevitably undergo the transformation of hæmoglobin referred

to, *i.e.*, into the primary hæmochromogen, which soon drops its iron, leaving as end-product bilirubin.

We have here the identical process that occurs in the brain or other structures when blood-clots are disorganized into hæmatoïdin preparatory to absorption. "The bile-pigments originate from hæmoglobin," says Professor Howell; "this origin was first indicated by the fact that in old blood-clots or in extravasations there was found a crystalline product, the so-called 'hæmatoïdin,' which was undoubtedly derived from hæmoglobin, and which, upon more careful examination, was proved to be identical with bilirubin. This origin, which has since been made probable by other reactions, is now universally adopted." That the influence of the suprarenal secretion rests upon as solid a foundation is illustrated by the experiments of Boinet, who found the blood of a large number of rats from which he had removed the adrenals replete with "hæmatoïdin."

To trace the itinerary of the two products, iron and bilirubin, through the liver, naturally brings the hepatic cell within the scope of our inquiry, since we have to account for the transfer of the former to the bile and the return of the iron to the general circulation.

The functional importance of iron in the hæmoglobin molecule is generally recognized. Yet, the pigments, when separated from it, are not unable to take up oxygen. Indeed, we have ample evidence of this in the formulæ of the very products of which bilirubin is the primary compound. Thus, while bilirubin is $C_{16}H_{18}N_2O_3$, biliverdin is $C_{16}H_{18}N_2O_4$, and the latter can readily be prepared artificially from the former by oxidation. "It is supposed that, when the blood-corpuscles go to pieces in the circulation," says Howell, "the hæmoglobin is brought to the liver, and then, under the influence of the liver-cells, is converted into an iron-free compound: bilirubin or biliverdin. It is very significant to find that the iron separated by this means from the hæmoglobin is, for the most part, retained in the liver, a *small portion* only being secreted in the bile. It seems probable that the iron held back in the liver is again used in some way *to make new hæmoglobin* in the hæmatopoietic organs." We have seen that *it is not under the influence of the liver-cells, as now believed, that hæmoglobin is dis-*

sociated: an important feature, since it removes the main element of confusion from our path. Indeed, we can now easily account for the retention of the greater part of bilirubin in the liver, since we have at our disposal all the constituents for the synthetic production *within* the portal capillaries of the hepatic lobule of new hæmoglobin, and particularly oxidizing substance, brought there by the terminals of the hepatic artery.

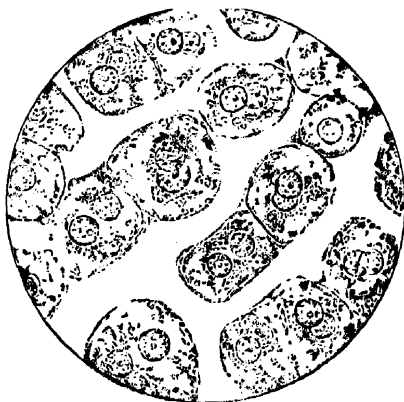
On examining, on page 329, the illustration from Piersol's work, the distribution of the hepatic artery's terminal arterioles or capillaries will be found to be unusual. Immediately above the margin of the lobule—*i.e.*, where the portal or interlobular vein breaks up into the capillary net-work of the lobule—the hepatic arteriole may be seen to open *into* the portal capillary. The inference is obvious. *The hepatic artery coming directly from the cæliac axis, brings freshly oxidized blood,—i.e., oxidizing substance,—which, mixing freely in the narrow channels of the lobule with the portal blood, at once groups bilirubin and iron, and builds up all the hæmoglobin that the constituents present (including what iron the splenic leucocytes and those from the intestinal follicles have brought) allow. What bilirubin cannot, owing to deficiency of either of the other constituents, be utilized, becomes an excretory product; and with many others it enters the hepatic CELL and is passed out with the bile.*

That deficiency of oxidizing substance (adrenoxidase) can increase the excretion of bilirubin has been repeatedly shown herein. I may refer, for example, to the many forms of acute poisoning and to the diseases attended with suprarenal insufficiency in which there is increased excretion, either in the urine or faeces, of hæmatoporphyrin, methæmoglobin, urobilin, stercobilin, etc.: *i.e.*, of some derivative of hæmoglobin.

I have referred to the hepatic cell as a miniature sponge. This comparison, due to Berdal, is especially warranted, since Schäfer⁴⁷ noted the existence, within this cell, of canaliculi which are in direct communication with the blood-capillaries. Having injected carmine gelatin into the portal vein, the colored substance filled this vessel and its subdivisions, besides the canaliculi, but no other structure. It may, therefore, be

⁴⁷ Schäfer: *Journal of Physiology*, Jan. 31, 1902.

inferred, says Professor Schäfer, "that the injection has passed directly from the blood-vessels into the liver-cells; indeed, here and there one can see what appear to be such direct communications." These can readily be seen in the annexed illustration. He refers to the conclusion reached by Browicz,⁴⁸ based on appearances, normal and pathological, "that there must exist a net-work of nutritive *canals* within the hepatic cells which are in direct communication with lobular capillaries"; this he had not as yet, however, verified by injections. Schäfer's observation probably accounts for the direct transfer of the bilirubin to the biliary capillaries, along with other



LIVER OF RABBIT INJECTED FROM THE PORTAL VEIN. THE INJECTION HAS PASSED INTO CANALICULI WITHIN THE LIVER-CELLS. (E. A. Schäfer.)

products of oxidation, to which we will refer later on. Indeed, J. W. and E. H. Fraser⁴⁹ are also stated to have found intracellular *passages* communicating with the blood-vessels in the hepatic cells of frogs. For the present it seems logical to conclude that one or more of the canaliculi may lead to the vacuole previously referred to as nearest the bile-capillaries, and that it is in this vacuole that bilirubin joins the bile. That even this vacuole is supplied with a canaliculus we have already

⁴⁸ Browicz: Bulletin de l'Académie des Sciences de Cracovie, 1893.

⁴⁹ J. W. and E. H. Fraser: Journal of Anatomy and Physiology, vol. xlix, p. 240, 1895.

seen; Kupffer found it to afford a direct channel between this bile-reservoir and the bile-capillaries *per se*.

The Hepatic Tissues in their Relations to Bacteria.—A prominent feature of the work so far done is the evidence furnished that several physiological processes now ascribed to the hepatic cell in no way involve this structure, and that the portal vein itself and the *intercellular*⁵⁰ capillaries are the seat of several of these processes.

Before proceeding further, however, reference must be made to the connection between bacteria and the *normal* liver. I emphasize “normal” here, because I can thus simultaneously lay stress upon a feature which plays a predominating rôle in disease: *i.e.*, the fact that anatomically, as far as bacteria go, there is no direct normal connection between the digestive system and this organ. The liver, in fact, is essentially a physiological organ in the sense that it is mainly intended to rid the system of waste-products and to economize others that may again prove useful, by preparing them for reabsorption in the intestine.

We have seen that the venules of the villi allow iron-pigment leucocytes to enter the mesenteric veins which carry their blood to the portal. A depraved condition of all the digestive structures—such as that induced by alcoholism, for instance—can so lower the functional activity of these structures as to cause these venules to lose their normal turgescence and afford passage to bacteria, alcohol in large doses being known to impair metabolism. The intestinal venules under these circumstances, surrounded by weakened protective structures, can well give passage to Adami’s cirrhosis bacillus, for instance, or any other capable of coping with what prophylactic conditions may still prevail. “The portal vein can transport to the liver morbid germs from the intestinal surface,” says Labadie-Lagrave. “One of the best established pathogenic connections of this kind is the influence exerted upon the development of hepatitis by dysentery; although this relationship is not constant, all observers have noted it. Phlebitis

⁵⁰ We find it necessary to give the terminals of the portal this name in order to avoid confusion; they contain blood from both the portal and hepatic channels, and in reality form part of both as extensions.—S.

starting from an ulcerated area and directed toward an hepatic focus has also been observed. When the primary portal structures are normal, transmission of the putrid material may occur through the lymphatics. While this fact seems admissible, it has not been verified." Again, pathological conditions of the stomach, pancreas, or spleen may supply the portal vein with pathogenic elements. In the normal subject, however, *the liver-tissues per se are totally isolated anatomically from any of the structures that come into contact with exogenous bacteria*, precisely as they are in other organs: the muscles, the heart, etc. That its blood-stream affords protection from disease is undoubted, however, judging from the leucocytes that are constantly entering the organ, and the perivascular lymphatic channels. That the portal vein is also an important field for the splitting of toxalbumins and their reduction to harmless bodies we shall also see. But it seems quite clear that the liver itself is not primarily a germ-killing organ, and that its attributes are essentially chemical. This removes the hepatic cell still further from the functions now attributed to it, and suggests that the oxidizing substance in the lobular blood-vessels may be the main source of the liver's functional activity.

This brings us to the consideration of the functions in which the oxidizing substance in the blood-plasma acts as a reagent. We have already reviewed, in this connection, the synthesis of hæmoglobin; we will now take up and consider two equally important subjects: *i.e.*, the origin of urea and the conversion of sugar into glycogen.

Urea and its Formation.—We will first analyze an experiment by Schröder⁵¹ in which the liver was taken from a freshly-killed dog and irrigated through its blood-vessels by a supply of blood taken from another animal. Howell refers to this experiment in the following words: "If the supply of blood was taken from a fasting animal, then circulating it through the isolated liver was not accompanied by any increase in the amount of urea contained in it. If, on the contrary, the blood was obtained from a well-fed dog, the amount of urea con-

⁵¹ Schröder: *Archiv für exper. Pathol. und Pharm.*, Bd. xv and xix, 1882 and 1885.

tained in it was distinctly increased by passing it through the liver, thus indicating that the blood of an animal after digestion contains something that the liver can convert to urea."

Considered from my standpoint, this experiment has another meaning. During digestion, especially after copious feeding, as stated above, the entire organism is, to a certain degree, involved in the digestive process, as shown by the general sensation of heat often experienced after such a meal. As liver, intestines, pancreas, and spleen, even after gastric digestion has passed, are all operating together, the suprarenal activity is doubtless enhanced. In other words, at such times the blood contains either in its corpuscles or in its serum a more or less marked increase of oxidizing substance. Conversely, the fasting dog's blood—especially if the fasting has been prolonged—is really abnormal blood, in which the oxidizing substance is unusually low, since suprarenal activity is depressed with that of the rest of the tissues. We have also seen that, under these conditions, the tissues nevertheless continue to absorb their normal supply of oxygen, the blood being thus actively depleted while insufficiently oxygenated. It seems clear, therefore, that the blood of the well-fed dog contained more oxidizing substance than that of the fasting one.

That the injected blood taken from the well-fed animal should have been the source of the urea-forming substance is unlikely. Since the liver alone receives alimentary waste-products, it is only with blood from the portal vein that such substances could have been obtained. This is not specified. The urea-forming agent must, therefore, have been in the excised liver's portal channels, and the only available agency capable of inducing the reactions involved appears to be the oxidizing substance. Experimental evidence may be adduced to show that such is the case. I consider the blood of the hepatic artery, as previously stated, as the source of supply of the oxidizing substance, since it is directly derived from the coeliac axis. Stewart states that, "although the portal vein carries a much greater supply of blood than the hepatic artery, *ligation of the latter* causes a greater diminution in the ratio of the amount of urea to the total nitrogen in the urine than

ligation of the former. This seems to indicate that oxidation plays an important part in the formation of urea in the liver (Doyon and Dufourt)."

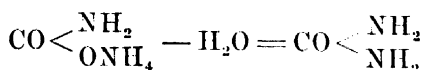
That the substances thus oxidized reach the liver by the portal vein needs hardly to be emphasized. But Foster says: "The introduction of even a small quantity of proteid material into the alimentary canal at once increases the urea in the urine, and in the curve of the discharge of urea in the twenty-four hours each meal is followed by a conspicuous rise. . . . We have seen reason to think that the proteids of a meal are absorbed not by the lacteals, but by the portal blood-vessels, and such bodies as leucin probably take the same course. This being so, all these bodies pass through the liver and are subjected to such influences as may be exerted by the hepatic cells."

Such bodies of leucin—one of the main products of nitrogenous dissociation—naturally follow the same course. Drechsel has suggested that all bodies of this class—*i.e.*, leucin, tyrosin, glycocoll, etc.—first undergo oxidation in the tissues, and that their ammonia and carbonic acid then combine synthetically, forming ammonium carbamate, this, in turn, being carried to the liver and there transformed into urea.

It is clear that these ammonia compounds take the course outlined by Foster: *i.e.*, the venules of the villi; the mesenteric veins, and finally the portal vein. That they undergo oxidation in the blood of these vessels, however, is not likely, for they contain probably the most watery blood of the organism, and that most depleted of its oxygen.

Quite another field of activity is afforded, however, when the hepatic lobule is reached; *here the ammonia compounds meet the oxidizing substance brought by the hepatic artery's capillaries*. Taking the ammonium compound referred to by Drechsel, for example, the series of reactions outlined by him seem to follow in normal sequence: 1. In the portal vein: hydrolytic cleavage with the formation of amido-bodies, such as leucin, tyrosin, aspartic acid, glycocoll, etc. 2. In the hepatic-lobule capillaries and their oxidizing substance: oxidation, with the formation of ammonia, carbonic acid, and water, followed by the synthetic union of ammonia and carbonic acid,

forming the carbamate of ammonium. This being dehydrated, urea is formed, as shown in the following equation:—



That the conversion of ammonia compounds into urea does occur in the liver is sustained by experimental physiology. Howell refers to the experiments of Schröder, in which this is demonstrated as follows: "As further proof of the urea-forming power of the liver, Schröder found that if ammonium carbonate was added to the blood circulating through the liver—to that from the fasting as well as from the well-nourished animal—a very decided increase in the urea always followed. It follows, from the last experiment, that the liver-cells are able to convert carbonate of ammonium into urea. The reactions may be expressed by the equation:—



The foregoing facts, considered collectively, indicate that the formation of urea in the liver is probably accomplished in the following manner, taking Dreesel's series of reactions as standard of the numerous ones of the same class that must occur in this organ:—

Granting that the *nitrogenous* bodies are absorbed by the venules of the intestinal villi and transmitted by the mesenteric veins to the portal vein, the ramifications of which would then carry them to the hepatic lobules, *the first reaction would occur in the prelobular portal vessels: i.e., the nitrogenous bodies would undergo hydrolysis, with the formation of amides, leucin, aspartic acid, tyrosin, etc.* The second reaction would follow as soon as these bodies reached the pericellular capillaries, owing to the presence therein of the oxidizing substance supplied by the terminal branches of the hepatic artery; in other words, *further reduction of these bodies by oxidation to ammonia, carbonic acid, and water would occur in the pericellular capillaries of the lobule.* The third reaction would seem, like the first, to require comparatively inert surroundings: *i.e., a fluid not charged with oxidizing substance as is the blood of the pericellular capillaries.* Such a medium we have, in all likelihood,

in the afferent venous channels, since it is very improbable that any oxidizing substance, so precious in all physiological functions—as I have now shown—should be wasted in vessels ultimately ending, *via* the hepatic veins, in the inferior vena cava. Hence, whether it involved a preliminary formation of an ammonic carbamate or proceed to immediate synthesis, *it appears as if the terminal reaction ending in the formation of urea occurred in the efferent venous hepatic channels.*

The salient point of this series of reactions is the fact that, contrary to the general belief, they all *occur, not in the hepatic cells, but in the blood-stream of the lobular capillaries.* The following facts show this to be the case: It is clear that, if urea is formed in transit through the vessels of the organ, it should appear as soon as, or at least soon after, its causative agencies are introduced in the portal system. We will recall the quotation from Professor Foster's text, in which he says: "The introduction of even a small quantity of proteid material into the alimentary canal at once increases the urea in the urine, and in the curve of the discharge of urea in the twenty-four hours each meal is followed by a conspicuous rise, etc." When we consider that the entire circulatory circuit occupies but twenty-six seconds, the cause of the rapid appearance of urea—heretofore unexplained—becomes apparent.

When the rôle of the oxidizing substance in the production of uric acid from the alloxuric bases was analyzed in the third chapter, uric acid was considered as the end-product of a series of reactions in which, according to modern views, these toxic nuclein derivatives were converted into benign ones. All nitrogenous products being transferred to the portal system, it now seems clear that normally the reaction must occur in the intercellular capillaries of the hepatic lobules, and that it is when this oxidation process in the liver is inadequate that the so-called "uric-acid diathesis" symptoms occur. As uric acid leaves the organism, as does urea, by the urine, it is evident that we are again dealing with a function totally disconnected from the hepatic cell *per se*. Again, we have repeatedly seen, in the preceding chapters, that the elimination of phosphoric acid was increased by the administration of suprarenal, pituitary, and other organic extracts and by various

drugs. As we have seen, increased excretion by the kidneys due to drugs always coincides with suprarenal overactivity, hence with enhanced oxidation. It thus becomes apparent that *many constituents of the urine, normal and abnormal, the origin of which is obscure, are connected with variations in the oxidation processes in the intercellular capillaries of the liver, caused by corresponding fluctuations in the functional activity of the adrenals.*

Glycogen and its Formation.—Glycogen obviously removes our inquiry from the arteriole to the hepatic cell, since this organ is that in which it accumulates; but we must not lose sight of the important fact that two processes are involved in the analysis,—(1) the formation of the glycogen and (2) its conversion into dextrose,—and that the latter reactions must occur in the vascular channels. Again, the first process seems so bound up with the formation of the bile that it becomes necessary to consider this subject simultaneously to avoid repetition.

The sponge-like construction of the hepatic cell due to its vacuoles, the delicate canals described by J. W. and E. H. Fraser, Browicz, and Schäfer, and, finally, the bile-collecting vacuole, or vesicle, leading through its own canaliculi to the perilobular bile-capillaries, does not appear to afford much room for protoplasm capable of undergoing functional metabolism, since this would have to be embodied in the partitions separating all these cavities. Yet, were it otherwise, the nucleus—often duplicated, particularly in herbivorous animals, almost one-third in size that of the entire cell, and containing nucleoli—would represent a useless structure. It seems evident, judging by the appearance of the cell as a whole, therefore, that the nucleus, which, as we have seen, is surrounded by a thin limiting layer of protoplasm, must impart its energy to this layer. This, in turn, being the central terminal of all the partitions, which, along with the cell's own pseudocovering, are protoplasmic, the vacuoles become receptacles, as it were, of the products of their walls.

Again, when we behold the minute canals so clearly shown in Schäfer's illustration (shown on page 340) a direct communication with parts external to the cell is evident in several

places, and it seems clear that, if his carmine gelatin could penetrate through these, so could an equally viscid substance, and with still greater ease, the blood-plasma. As "no injection in the intercellular bile-canalliculi nor in the perivascular lymphatics nor between the cells" could be detected, the penetration of the gelatin can hardly be ascribed to undue stress. "There being," also, "no diffusion of carmine nor any staining of the cells or nuclei by carmine," the nucleo-mural network to which I refer must be an independent structure, circumscribing two kinds of cavities: the canals and the vacuoles. The canals communicating with the exterior of the cell, they are probably the receiving cavities, while the vacuoles, their neighbors, are the spaces in which the *useful* products of metabolism are accumulated. The canals themselves, continuing until Kupfer's vesicle is reached, would thus pour their excretory contents—bile and its various constituents—into this cavity, and this, in turn, would convey them to the intercellular bile-capillaries through its own canals.

Whether so direct a connection between the intercellular capillaries and the bile-channels through the cell exists is a point to be determined. Bile and the various bodies excreted with it would be voided as are the intestinal contents, the canalicular walls taking up certain elements, while physiological substances would be mixed with the substances in transit for definite purposes.

The first question that suggests itself is the following: Is glycogen formed during the *active* functional activity of the liver (during digestion) or during its *passive* state (between meals)? We have seen that the production of urea is increased immediately after a meal; we have evidence, therefore, that an active state based upon increased oxidation processes must prevail, and that it is during digestion that the substances out of which glycogen is formed reach the liver, *i.e.*, while the oxidizing substance is present in the capillaries. This suggests that the oxidizing substance must itself take part in the formation of glycogen, though perhaps *indirectly*, and also in the elaboration of bile.

The main coloring constituent of bile, bilirubin, I have previously considered as the product of a reaction in the inter-

cellular capillaries. As such it is probably eliminated with the bile merely because its high oxygen constituent places it beyond the limits of further oxidation. Yet we have in another component of bile, biliverdin, evidence that some oxidizing process occurs during the passage of bilirubin through the cell, under certain circumstances,—perhaps when more oxidizing substance is present,—for Howell says: “Biliverdin is supposed to stand to bilirubin in the relation of an oxidation product. Bilirubin is given the formula, $C_{16}H_{18}N_2O_3$, and biliverdin, $C_{16}H_{18}N_2O_4$, the latter being prepared readily from pure specimens of the former by oxidation.”

With this evidence that oxidation does play some rôle of the processes involved, it will facilitate my task to briefly review the mutual relations of main biliary constituents. By far the larger proportion of these is made up of the bile acids, namely: the sodium salts of cholic acid,—*i.e.*, glycocholic and taurocholic acid. These are obtained from cholic acid *derived itself from sugars and fats* (Voit). Now, Tappeiner⁵² found that cholic acid yielded fatty acids *on oxidation*, and, since taurocholic and glycocholic acids are fatty acids, this suggests that they become such during their passage through the hepatic cells and as the result of an oxidation process.

The various phases of the process in the hepatic cells become clear when the oxidizing substance is included as one of the intrinsic factors involved. The blood-plasma of the portal vein contributes the sugars and fats (along with the waste-products to be excreted), while the hepatic artery supplies plasma containing the oxidizing substance. All three active agents meeting in the canaliculi, a part of the sugar (according to the proportion of oxidizing substance present) and all the fat (if the proportion of oxidizing substance is not abnormally reduced by suprarenal insufficiency) are oxidized into cholic acid. But, as the blood also contains glycocoll (probably collagen-cartilage, mucin, connective tissue, and gelatin-waste), glycocholic acid is formed. Again, since the blood likewise contains taurin (probably muscle and pulmonary-tissue waste), taurocholic acid is formed. Just the amount of oxidizing substance necessary being supplied by the hepatic

⁵² Tappeiner: *Zeitschrift für Biologie*, Bd. xii, S. 60, 1876.

artery to each lobule, to properly regulate the functions involved, only the required sugar is burnt by the oxidizing substance. The rest, under the influence of the nuclei of the hepatic cells and the mural protoplasm of the latter, is converted into glycogen and collected in the adjoining alveoli.

But we must also account for the elimination of the many waste-products that are found in bile. An interesting feature connected with these fatty acids is that they can combine synthetically with other bodies, even with proteids, while they are simultaneously able to emulsify the more insoluble soaps and other fatty acids and thus insure their elimination. Again, cholesterin, mainly derived from the white matter of the cerebro-spinal axis and nerves (Flint), in which it occurs in abundance (Foster), was formerly considered as a fatty substance capable of undergoing saponification, but it is now classed among alcohols: the only alcohol that occurs in the organism in a free state. This body is not only soluble in solutions of the biliary acids also, but it *combines* with acids, including glycocholic acid. The importance of this fact appears when it is recalled that insufficiency of glycocholic acid in this connection—and also, perhaps, of oxidizing substance—is the main source of gall-stones. The cholesterin being a constant constituent of bile, when there is not enough glycocholic acid present to take it up, it is precipitated in the gall-bladder and there forms the calculi of which it is the main component. Another body derived from nervous structures, but which, like cholesterin, is to be found in other fluids, especially blood-serum, is lecithin. This body, besides others not mentioned, only occurs, however, in very limited proportions.

It is now evident that glycocholic acid and taurocholic acid should be looked upon as *functional* acids, in the sense that they are not only vehicles for waste-products of metabolism, but are also capable of submitting them to dissociating reactions under the influence of the oxidizing substance. They are sources of energy precisely as myosinogen appears to be a source of energy, and capable of becoming factors of combustion phenomena when in contact with the latter substance. They are also truly physiological in the sense that they serve to recover or economize those products which can again be

used by the organism. Indeed, they (or at least a part of their decomposition products) are again absorbed by the intestinal mucous membrane, and, passing through the venous channels, probably take up therein and transfer to the hepatic cells what waste-matter they are to carry to the intestinal tract. We thus have in the cellular canaliculi two acids endowed with powerful affinities and an active reagent, the oxidizing substance, to account for the processes of a chemical nature connected with the functions of the hepatic cell.

Of course, all this involves the necessity of showing, as a controlling factor, that products of combustion are also present. The following lines by Professor Howell give this feature due emphasis; referring to bile, he says: "The secretion contains also a *considerable, though variable, quantity of CO₂ gas*, held in such loose combination that it can be extracted with a gas-pump without the addition of acid. The presence of this constituent serves as an indication of the extensive metabolic changes occurring in the liver-cells."

Again, the element of nervous control implied when I referred to the oxidizing substance contributed by the hepatic artery must be shown. We have seen that the vagus was the *active* nerve during functional activity of the stomach; that it should likewise govern hepatic functions is obvious. That such is the case is sustained by no less an authority than Claude Bernard, to whom we owe the discovery of glycogen—one of his greatest achievements—and whose conceptions have been almost all sustained by all the labor bestowed upon them since. He not only found that the vagus was the predominating nerve in the liver, but that its section also suppressed its glycogenic function.

The fate of glycogen, its conversion into sugar for the use of muscular and other tissues, may now be analyzed with greater facility.

My analysis of muscular functions led me to the deduction that the contractile elements contained a substance, myosinogen, which, when brought into contact with the oxidizing substance of the plasma, became the source of the muscle's working energy. Ample evidence was afforded to show that we were dealing with an oxidation process, the intensity of which

was commensurate with the amount of blood that the arterioles supplied to the contractile tubular elements. There seems to be considerable analogy between this process and that which prevails in the hepatic lobule. Howell alludes to this in the following words, which well recall the fact that we referred to glycogen as the main constituent of myosinogen: "The history of glycogen is not complete without some reference to its occurrence in the muscles. Glycogen is, in fact, found in various places in the body, and is widely distributed throughout the animal kingdom. It occurs, for example, in leucocytes, in the placenta, in the rapidly-growing tissues of the embryo, and in considerable abundance in the oyster and other mollusks. But in our bodies and in those of the mammals generally the most significant occurrence of glycogen, outside the liver, is in the voluntary muscles, of which glycogen forms a normal constituent."

The similarity between muscular and hepatic sources of energy is further emphasized when, in the following paragraph, Howell says: "In accordance with the view given above of the general value of glycogen—namely: that it is a temporary reserve-supply of carbohydrate material that may be *rapidly converted into sugar and oxidized*,⁵³ *with the liberation of energy*—it is found that the supply of glycogen is greatly affected by conditions calling for increased metabolism in the body. Muscular exercise will quickly exhaust the supply of muscle and liver glycogen provided it is not renewed by new food. In a starving animal glycogen will finally disappear, except perhaps in traces; but this disappearance will occur much sooner if the animal is made to use its muscles at the same time. It has been shown also by Morat and Dufourt that, if a muscle has been made to contract vigorously, it will take up much more sugar from an artificial supply of blood sent through it than a similar muscle which has been resting; on the other hand, it has been found that, if the nerve of one leg is cut so as to paralyze the muscles of that side of the body, the amount of glycogen will increase rapidly in these muscles as compared

⁵³ The italics are our own.

with those of the other leg, that have been contracting meantime and using up their glycogen."

These facts clearly indicate that oxidation processes are not in order here, since glycogen is a source of energy, intended, therefore, for subsequent oxidation wherever it is distributed. Indeed, Professor Foster remarks, in this connection: "It was formerly believed that this sugar underwent an immediate and direct oxidation as it was circulating in the blood. . . . It is sufficient for us at the present to admit that the sugar is made use of in some way or other." Referring to the physiological uses of glycogen, he also says: "The main purpose of the deposition of glycogen is to afford a store, either general or local, of carbohydrate material, which can be packed away without much trouble so long as it remains glycogen, but which can be drawn upon as a source of soluble circulating sugar whenever the needs of this or that tissue demand it." That the oxidizing substance has nothing to do with the process is clear.

The conversion of glycogen into sugar in the liver appears as a wasted function, the carbohydrates having been already split into dextrose or dextrose and levulose in the portal system. Why they do not merely pass on to the several tissues seems strange. But it soon becomes evident that, were it otherwise, sugar would accumulate, then be excreted by the kidneys, and lost, since there can only be a fixed and limited (0.1 or 0.2 per cent.) amount of sugar in the circulation at a given time. So useful a substance is, therefore, stored, after dehydration, in the hepatic cell as glycogen, and converted into sugar according to the needs of the organism.

Conversion of the liver glycogen into dextrose is generally ascribed to a special ferment, thought to originate in the liver, but the nature of which has remained undetermined. The experiment of Claude Bernard, upon which this view is mainly based, is the following, as related by Stewart: "A rabbit, after a large carbohydrate meal—of carrots, for instance—is killed and its liver rapidly excised, cut into small pieces, and thrown into acidulated boiling water. After being boiled for a few minutes the pieces of liver are rubbed up in a mortar and again boiled in the same water. The opalescent aqueous extract is

filtered off from the coagulated proteids. No sugar, or only traces of it, is found in the extract, but another carbohydrate—glycogen, an isomer of starch, giving a port-wine color with iodine and capable of ready conversion into sugar by amylolytic ferments—is present in large amount. Again, the liver, after the death of the animal, is left for a time *in situ*, or, if excised, is kept at a temperature of 30° to 40° C. or for a longer period at a lower temperature; it is then treated exactly as before, but no glycogen, or comparatively little, can now be obtained from it, although sugar (dextrose) is abundant. The inference plainly is that after death the hepatic glycogen is converted into dextrose by some influence which is restrained or destroyed by boiling. This influence may be due to *an unformed ferment* or to the *direct action of the liver-cells*, for both unformed ferments and living tissue-elements are destroyed at the temperature of boiling water.”

Another explanation suggests itself to me if, instead of a ferment of hepatic origin, we hypothetically use one of external origin: In the first procedure immediate immersion in boiling water destroyed the ferment which happened to be in the blood-vessels, while, in the second, the ferment was given time to act. The difference in the conclusions vouchsafed is simply this: no thought being given to the blood-vessels, the ferment could only be considered as of cellular origin. We have seen how many functions ascribed to the hepatic cells really belonged to the intercellular blood-stream; this seems to be an additional one.

Admitting that we are dealing with a ferment of external origin, from which organ could we expect it to be derived? Can we attribute the process to ferments from the salivary glands or pancreas? If it is produced only by digestive ferments,—*i.e.*, amylolytic ferments poured out during digestion,—why does glycosuria appear irrespective of any digestive process when the floor of the fourth ventricle is punctured, as shown by Claude Bernard? He also found that conversion of glycogen into sugar was a continuous process, carried on to subserve the needs of the organism: a perfectly logical conclusion if the liver is really a storehouse for this substance. Again, the quantity of sugar in the blood, as we have seen,

is small, but constant. How could we account for these features of the problem with ferments transmitted through the digestive tract?

Finally, sugars thus produced—*i.e.*, from amylolytic ferments secreted by the digestive tract—do not seem to be dextrose, the sugar produced by the supposed hepatic ferment. Thus, Professor Foster says: "In the case of the amylolytic ferment of saliva, pancreatic juice, intestinal juice, and, indeed, of all other amylolytic animal fluids, the sugar into which starch or glycogen is converted is *mallose*. Now, the sugar which appears in the liver after death is dextrose, identical, as far at least as can at present be made out, with ordinary *dextrose*." It is evident that a ferment other than the amyl-opsin connected with the digestive process must be the active one, and that it must reach the liver by a channel other than the intestinal tract, the villi, etc. Again, it must be very nearly similar to the salivary and pancreatic amylolytic ferments. The salivary glands are so remote anatomically that they can hardly be considered; we are brought, therefore, to the pancreas as the only organ which could act as source of a ferment or diastase having for its main function to convert glycogen into dextrin.

As shown by von Mehring, Minkowski, and de Dominicis, removal of the pancreas causes marked glycosuria, and this persists whether the animal be given carbohydrates or not. All the other symptoms of diabetes mellitus appear,—namely: increased flow of urine, considerable urea, acetone, etc.; great thirst and hunger, emaciation, marked muscular weakness,—followed by death in two to four weeks. Indeed, we are vividly reminded of the suprarenal glands, on ascertaining that grafting of a piece of pancreas in the abdomen or skin will arrest the glycosuria, and that, if a small portion of the organ is left, the symptoms will disappear. Again, whether carbohydrates are given as food or not, the glycogen disappears from the liver. "We may believe, from these experiments," says Howell, "that the pancreas produces a substance of some kind that is given off to the blood or lymph, and is either necessary for the normal consumption of sugar in the body or else, as is held by some, normally restrains the output of sugar from the

liver and other sugar-producing tissues of the body. What this material is and how it acts has not yet been determined satisfactorily." That we are dealing with an internal secretion is clear, and, such being the case, the secretion probably passes out into the blood by the pancreatic vein, which "opens into the splenic and mesenteric veins." As these open, in turn, in the portal vein, the pancreas would then supply a special ferment for the conversion of glycogen into a functional sugar.

If the foregoing symptoms are closely scrutinized, it soon becomes apparent that the functions of the pancreas—as will be shown in the next chapter—are far more important than is generally believed. For the present, however, we will limit our inquiry to the subject in point.

The fact that, notwithstanding the ingestion of carbohydrates, the glycogen will totally disappear from the liver is easily accounted for. A prominent function of the pancreas during intestinal digestion is to transform starches into maltose, to insure absorption of this sugar. When the organ is removed, therefore, its amylopsin is no longer furnished to the intestinal contents, starches are not properly converted, and the portal vein carries no maltose to the hepatic lobule. The production of glycogen, therefore, ceases. The fact, however, that we can so easily account for this phenomenon suggests that:—

1. *The pancreas is the organ upon which all the preliminary functions connected with the formation of glycogen depend.*

2. *Its amylopsin converts starches in the intestine to prepare them for the elaboration of glycogen in the hepatic cell.*

3. *Its internal secretion, supplied to the portal system by way of the splenic vein, converts glycogen into dextrose.*

That we are on the right path is suggested by a series of experiments by Croftan,⁵⁴ in which the conversion of glycogen into sugar was obtained by means of injections of suprarenal extract: "Incomplete as these experiments are," says the author, "they reveal the fact that the injection of suprarenal extract can cause the excretion of dextrose provided the quantity injected is sufficiently large. Why in the case of one

⁵⁴ Croftan: *American Medicine*, Jan. 18, 1902

animal more must be given than in the case of another to produce approximately the same excretion is undecided and remains to be determined." Dwelling upon the presence in the adrenals of a diastatic ferment, he states that "two possibilities may present themselves, viz.: either the suprarenals manufacture a diastatic ferment or they retain the diastatic ferment that is formed elsewhere in the body (pancreas, salivary glands) when it is carried to them in the blood- or lymph- stream." The author also refers to the investigations of F. Blum,⁵⁵ who, "testing the effects of suprarenal extract empirically," discovered "glycosuria in 22 out of 25 animals that he operated on." My interpretation of the manner in which these investigators reached their results is, of course, not that of Croftan, since, as I view the process, the oxidizing substance constitutes the active suprarenal agency as a compound of suprarenal secretion and oxygen.

We are dealing with enhanced physiological activity *somewhere*. Indeed, Croftan says: "In order that hyperglycosuria be produced the amount of sugar normally poured into the blood must be increased, or the amount normally destroyed must be decreased." That excessive activity was either procured by the injected extract or by overstimulation of the adrenals, both leading to total insufficiency, is shown by the brief history of one of the animals: "The second rabbit died in one hour and ten minutes; here some *spasmodic* symptoms, involving chiefly the *posterior* extremities, preceded the coma." Referring to two rabbits, including the latter, the first having died in two hours and forty minutes and to "all others to be spoken of presently" (six, all told), he says: "Dextrose was identified in the urine by its cupric-reducing powers and the phenylhydrazin test; in one of the dogs in addition by circum-polarization and yeast fermentation. The substance excreted was undoubtedly dextrose. The amount excreted would be far too large to be explainable by a splitting of the jecorin-like substance mentioned above; it would not, moreover, be possible for considerable quantities of dextrose derived from this source to appear in the urine for several days after the injec-

⁵⁵ F. Blum: *Deutsche Archiv f. klin. Med.*, Oct. 31, 1901.

tion." Excessive stimulation by a great increase of oxidizing substance in the blood evidently occurred. As soon as the extract was injected it was carried to the lungs, and lost its individuality immediately therein by taking up oxygen. It could no longer, therefore, act as a diastase.

The question now to decide is this: General stimulation enhanced the production of an amylolytic ferment either by the liver or by the pancreas. To which organ can we ascribe this function? Since oxidation destroys sugar, a great excess of oxidizing substance in the blood would burn sugar actively on all sides and produce the *opposite* of glycosuria: *i.e.*, excessive combustion and rapid disappearance of the liver glycogen through abnormal use of it in the other organs. But here we have, as a result of a great increase of oxidizing substance in the blood, marked glycosuria, and that evidently without preliminary feeding, since this fact is not mentioned by Croftan. As the oxidizing substance does not affect glycogen, that of the liver could not be converted by it into sugar; hence the excessive production of the latter can only be accounted for by an equally excessive production of amylolytic ferment.

Claude Bernard showed that conversion of glycogen into sugar took place more rapidly when the blood was made to traverse the liver with unusual speed. Yet he attributed the formation of the ferment to the liver, having obtained it from pulp rubbed up and treated with glycerin, after the liver had been washed out so as to remove the vascular contents. But it seems clear that injections by the portal vein will hardly deplete the liver of every particle of the ferment in its minute lobular capillaries, while reduction of its substance to pulp and a three days' immersion in glycerin will dissolve all that contained in the latter. When we consider how readily conversion can be produced,—even by traces of soluble albumin, according to Seegen,—it is evident that upon the addition of water to the glycerin solution the very small proportion that may have remained imprisoned in some of the lobules will suffice for the conversion of glycogen.

One of Claude Bernard's experiments seems to me to afford proof that the amylolytic ferment reaches the liver through

the portal vein. By ligating the latter vessel he created a collateral circulation, and shifted the portal-blood stream into the general circulation. Ten or 12 grammes of sugar were then given to the animal, and sugar was soon found in the urine. In a normal dog, on the other hand, 50 to 80 grammes had to be administered before this result was obtained (M. Duval⁶⁶). The absence of sugar in the latter animal's urine until a very large quantity of sugar had been ingested distinctly shows that conversion of its *glycogen* only occurred because its portal vein was open; in the other dog it was not converted glycogen that passed into the urine, but maltose, *i.e.*, intestinal starch which had been submitted to the action of the pancreas's intestinal ferment,—*i.e.*, amyllopsin. If we now couple the fact that conversion of liver-glycogen only occurs when the portal vein is free with Claude Bernard's observation that increased speed of the portal blood through the liver causes the glycogen to be converted more rapidly, it seems clear *that the conversion process is not due to an hepatic ferment, and that the pancreas supplies, as an internal secretion, the ferment which converts glycogen into dextrose.*

A perplexing feature of all this requires elucidation, however. If, as we have stated, the blood-plasma contains an oxidizing substance, why is the sugar not oxidized on its way to the tissues of distribution? Armand Gautier⁶⁷ refers to the investigations of Jaquet, which demonstrated that sugars mixed with blood containing the oxidation ferment previously referred to, and which we found to be of suprarenal origin, did not become oxidized. He ascertained, however, that upon adding to the blood a small quantity of fine pulp of muscle, lung, or of any other organ, the oxygen was absorbed. This obviously indicates that *dextrose passes through the blood without being destroyed, and it can only become oxidized after combining with bodies produced by the organs to which it is distributed.*

General Functions of the Liver, Spleen, and Pancreas.—All the facts reviewed in this chapter suggest the following conclusions as to the functions of the liver, spleen, and pancreas:—

⁶⁶ M. Duval: *Loc. cit.*, p. 378.

⁶⁷ Armand Gautier: "La Chimie de la Cellule Vivante," p.

1. *The hepatic artery, owing to the oxidizing substance (adrenoxidase) that its plasma contains and the mode of distribution of its terminal capillaries, supplies the exogenous chemical energy which initiates and sustains all reactions in the hepatic lobule that require oxygen.*

2. *The nervous supply of the liver is composed, first, of terminal subdivisions of the vagus, which enhance the activity of all its functions by causing dilation of the hepatic arterioles; and, second, of terminal subdivisions of the sympathetic, which, by causing constriction of these arterioles, reduce the functional activity of the organ.*

3. *In the normal subject the liver is anatomically isolated from structures that come into contact with bacteria, and protected against their intrusion by the bactericidal products of the intestinal glands and follicles.*

4. *The capillaries of the hepatic lobules, owing to the admixture therein of the hepatic artery's oxidizing substance (adrenoxidase) with the portal vein's waste-laden blood, are the seat of several functions now ascribed to the hepatic cell.*

5. *Blood-pigments and iron, derived from the intestine and spleen, simultaneously penetrate the hepatic lobule, and combine with the adrenoxidase therein to form hæmoglobin. The uncombined pigment is eliminated with the bile as bilirubin.*

6. *Urea is the end-product of three successive reactions, viz., (1) nitrogenous bodies are reduced to amides in the afferent veins,—mesenteric and portal; (2) the amides are dissociated into ammonia, carbonic acid, and water by the oxidizing substance (adrenoxidase) in the hepatic lobule; (3) urea is formed by synthesis in the efferent veins,—hepatic and vena cava.*

7. *The hepatic cell contains, besides its vacuoles and nuclei, numerous canaliculi (Schäfer) and a vesicular vacuole which opens into the bile-capillaries by a canaliculus (Kupffer); the canaliculi and the vesicular vacuole are probably connected.*

8. *Glycocholic acid and taurocholic acid are functional acids, inasmuch as they dissociate and appropriate waste-products, and, under the influence of the oxidizing substance, convert them into excrementitious products in the canaliculi of the hepatic cells.*

9. *The waste-products so converted by the biliary acids and the latter themselves, constituting bile, are transferred, along*

with other products for which the latter may serve as vehicle,—bilirubin, earthy salts, etc.,—to the vesicular vacuole of the cell and eliminated by the canaliculus that opens into the bile-capillaries.

10. *The biliary acids, blood-pigments, iron, and other bodies or any of their components, that may prove useful to the organism are, entirely or in part, reabsorbed by the intestinal venules and returned to the portal circulation.*

11. *The sugars converted from intestinal foodstuffs in the intestines are brought to the hepatic lobule with the portal blood, and penetrate the canaliculi with the latter and with the oxidizing substance. During the bile-forming reaction the sugars are dehydrated, and, probably with the assistance of the cellular protoplasm, converted into glycogen.*

12. *The liver glycogen is converted into dextrose by an amylolytic ferment supplied by the pancreas as an internal secretion, which enters the portal circulation by the splenic vein.*

13. *Dextrose is distributed to the organs in which it is used as a source of energy by the blood, and only becomes vulnerable to oxidation when combined with products of metabolism furnished by those organs.*

CHAPTER VIII.

THE INTERNAL SECRETIONS OF THE PANCREAS AND SPLEEN.

GLYCOSURIA AND OVERACTIVITY OF THE ADRENAL SYSTEM.

—The pancreas and spleen are considered together because there is considerable evidence in favor of the view that they are functionally associated; and it is to give the analysis of this question and its relationship with the ferments furnished by the pancreas to the portal blood due prominence that we have, under other headings, considered the better-known functions of both organs.

To sustain our belief that liver glycogen is converted into dextrose by an amylolytic ferment supplied by the pancreas which penetrates the portal vein directly,—*i.e.*, by way of the splenic vein,—we were fortunate in having at our disposal the experiments of Croftan, which showed that suprarenal overactivity could so augment the functional activity of the ferment-producing organ as to induce a very great increase in the sugar eliminated. This feature requires further study, since it will tend to elucidate other functions of the pancreas.

We believe that we have conclusively shown that certain drugs and poisons increase the functional activity of the adrenals. The uniformity of the phenomena traceable to these glands under the influence of such agents seems to us to warrant the conclusion that, if we can demonstrate that glycosuria is also subject to the latter, its fluctuations following those of the suprarenal activity or insufficiency induced by them, a direct connection between glycosuria and suprarenal overactivity will have been shown. Yet we must bear in mind, in this connection, that all active drugs *may* have a primary action upon tissues for which they possess a specific affinity before the suprarenal protective functions are fully awakened. We have seen that even electrical stimulation of the splanchnic is only followed by vermicular motions of the intestinal wall after some time elapsed. But too much weight must

not be given this feature, inasmuch as I have personally seen the typical symptoms of total suprarenal insufficiency occur in a dog within twenty seconds after a fatal dose of hydrocyanide of potassium had been administered. Large quantities of the less active drugs are more likely to reach the tissues for which they possess a special predilection, bromide of potassium, for instance, than such an agent as that previously mentioned. While, therefore, we cannot say that excessive formation of sugar, when drugs are given, is due only to overstimulation of the adrenals, we can say that all drugs can produce it when they stimulate suprarenal activity. Furthermore, it seems probable that some drugs not only do this, but they likewise, owing to their affinity for certain tissues, enhance the production of sugar by increasing the functional activity of the intimate structures of the organs concerned in its production from ingested substances—thus stimulating two different sets of organs simultaneously. Such an agent we probably have in phloridzin.

In an able and exhaustive review of the subject of toxic glycosuria, F. Cartier,¹ of Paris, says: "The symptomatology of phloridzin is very limited, seeing that it does not give rise to a true intoxication. . . . In man it is even possible to bring on glycosuria, and maintain it a long time, without giving rise to general disorders, provided a copious alimentation is insured." We have evidence in the last sentence that the main general result is an *excessive formation* of sugar, and, more carbohydrates being required, it is to an excessive production of the converting agent that we must ascribe this phenomenon. Still, if general symptoms are absent, what becomes of the suprarenal overactivity? Cartier answers this question when he says: "Yet *all* authors who have studied phloridzin unite in saying that the animal experimented upon becomes *voracious*, and, if not overfed, rapidly wastes. . . . When alimentation is insufficient, grave phenomena appear. Phloridzinic glycosuria has been obtained in animals entirely deprived of hydrocarbons; under these circumstances general symptoms *analogous to those of diabetic coma* have been observed."

¹ F. Cartier: Thèse de Paris, 1891.

Osler² states that Frerichs recognized three groups of cases; two of these are of special interest to us: (a) Those in which after exertion the patients were suddenly attacked with weakness, syncope, somnolence, and gradually deepening unconsciousness, death occurring in a few hours. (b) Cases with preliminary gastric disturbance, such as nausea and vomiting, or some local affection, as pharyngitis, phlegmon, or a pulmonary complication. In such cases the attack begins with *headache*, delirium, great distress, and *dyspnea*, affecting both inspiration and expiration: a condition called by Kussmaul *air-hunger*. *Cyanosis* may or may not be present. If it is, the *pulse* becomes *rapid and weak* and the patient gradually sinks into *coma*, the attack lasting from one to five days. The need of a copious supply of carbohydrates obviously points to increased oxidation. Indeed, complete absence of glycogen in the liver and muscles has been noted. The voracious appetite and rapid wasting further sustain this—and simultaneously, therefore, the presence of suprarenal overactivity. The italicized words in the list of terminal symptoms, on the other hand, as prominently point to the gradually deepening suprarenal exhaustion.

Alluding to the effects of acids in the production of glycosuria, Cartier refers to the experiments of Pavy³ with phosphoric acid. An increase of sugar was noted in twenty minutes; fifteen minutes later a large quantity was present. In another strong, but *fasting*, dog the sugar was markedly reduced by a smaller dose. Hemorrhagic infiltration of the gastric and intestinal tissues and hamaturia were also noted. These are all familiar landmarks of suprarenal origin. Striking, in this connection, are the observations of Stadelmann,⁴ who found that the production of CO₂ decreased in the rabbit during acid intoxications as it does in diabetic coma. In a foot-note Cartier says: "Voit and Pettenkofer and Gaethgens have peremptorily shown, by means of most precise experiments, that (1) the oxygen absorbed by a diabetic is much less than by a normal man, and that it decreases progressively until

² Osler: "Practice of Medicine," third edition.

³ Pavy: Guy's Hospital Reports, vol. of 1861.

⁴ Stadelmann: Deutsche med. Wochenschrift, Nov. 4, 1890.

the end of the disease, when it is hardly equal to half of the normal quantity; (2) that the CO_2 exhaled is likewise reduced." That this is essentially due to suprarenal insufficiency—i.e., reduced oxidation—is shown by the fact that, in a case of coma due to meningitis witnessed by Stadelmann, the proportion of CO_2 was 28.2 per cent.; while in diabetic coma the gradual decline is that observed in Minkowski's rabbits, which, from the normal 25 per cent., steadily dropped to 16, 8.8, then 2.9 per cent.

We have seen that tetanus was partly due to adrenal overactivity. Cartier refers to the experiments of Claude Bernard, which showed that strychnine produced glycosuria in dogs. "It is unnecessary to reproduce here," says Cartier, "the symptoms of poisoning produced by this alkaloid; we will simply say that nothing recalls tetanus to such a high degree as does intoxication by it." We have another proof that it is due to an excessive production of a ferment or some other agency possessed of converting powers since Langendorff found that "glycosuria only occurs in frogs when the liver contains glycogen. . . . In the summer, when their liver contains none, strychnine does not cause diabetes in these animals."

We are reminded of the disorganization of hemoglobin produced by advanced suprarenal insufficiency when, referring to curare glycosuria, Cartier says: "Others account for this glycosuria by an insufficiency of the respiration and by slowing of combustions. The dark coloration of curarized blood indicates this asphyxia." Even the nervous distribution, *as I interpret it*, including the basospinal connection between the pituitary body and the adrenals, finds itself sustained in a remarkable manner by the following lines of Cartier's in reference to morphine glycosuria: "An extremely interesting fact that all these investigations indicate is that one can produce with a toxic substance exactly similar phenomena to those recorded by Claude Bernard in his lessons at the College of France, and obtained by puncture of the medulla, and that these toxic glycosurias can in most cases be arrested, as are glycosurias of nervous origin, by severing the centrifugal nerve-impulse conductors. Indeed, section of the pneumogastric (centripetal nerve) does not prevent glycosuria caused either by Bernard's puncture or by morphine; but, on the contrary,

section of the splanchnic nerves (centrifugal nerves) and of the medulla above the origin of these nerves prevents both the experimental diabetes of Claude Bernard and the toxic diabetes caused by morphine."

The list of drugs that are able to produce glycosuria could be indefinitely prolonged: it includes all those that produce suprarenal overactivity. But this does not mean that the ferment-producing organ is alone stimulated; glycosuria is but one of the manifestations of the exaggerated *general* metabolism induced, and oxidation processes are enhanced accordingly. Toxic glycosuria, therefore, only represents the surplus of sugar which oxidation processes have not consumed; the excess of sugar actually produced is probably far greater than the surplus which the urine shows. Again, certain drugs—phosphorus, for instance—do not produce glycosuria to any marked degree; as soon as the dose capable of causing it is reached, the adrenals lapse into insufficiency, and, if the dose is pushed to any extent, even the normal ratio is reduced. Antipyrin is now considerably employed in diabetes; we have seen that this drug and acetanilid readily produced suprarenal insufficiency and dissociation of the hæmoglobin molecule. This is sufficiently extensive sometimes to manifest itself as methæmoglobinuria or even hæmatoporphyrinuria. All these facts seem to me to indicate that *toxic glycosuria is primarily due to overstimulation of the adrenal system, the excessive functional activity which increased oxidation produces giving rise to an inordinate production of an agency that converts glycogen into sugar.* All these features will again be reviewed.

That the agency which converts glycogen into sugar is the amylolytic ferment produced by the pancreas to which I have referred is further sustained by the foregoing facts, especially in view of the amylolytic properties of the pancreatic secretion in the intestine. Since the conversion into sugar occurs during fasting as well as during digestion under the effects of toxics, the reaction can only include the hepatic glycogen and pancreatic ferment; and, there being nothing in the intestine to convert during fasting, the ferment must necessarily reach the glycogen by another channel. *May this not be the more direct route afforded by the splenic vein?*

Yet there is a possibility that the flow of amylapsin in the intestine, which the enhanced activity of the pancreas must undoubtedly increase, may be reabsorbed by the venules, and, being carried into the portal system, produce conversion of the glycogen precisely as if it had entered the portal vein by the way of the splenic vein. But we have seen that, while removal of the pancreas is rapidly followed by death, very large portions of the gland can be safely removed. Admitting that the operators may have left the portions related with the pancreatic duct, how could we account for the effects of transplanted fragments in arresting the glycosuria caused by removal of the pancreas, recorded by Minkowski⁵ and Hédou?⁶ As long as fragments transplanted subcutaneously remained normal no glycosuria occurred; it reappeared, however, when these fragments became histologically impaired. It is evident that the only channel here for the amylolytic ferment produced could be the blood. Thus carried to the heart, it then penetrated the liver by way of the hepatic artery, and reached the intercellular capillaries and the glycogen precisely as if it had penetrated the organ by way of the portal vein. Although but a small quantity of the ferment could thus reach the liver, it was evidently sufficient to convert the amount of glycogen required to build up the very limited proportion of sugar found in the normal blood, as previously shown. Again, we have seen that the product of intestinal reduction is maltose, while the urine of Croftan's animals when stimulated with suprarenal extract gave dextrose in very great quantities: a feature denoting successive processes. This and the other facts adduced appear to me to contribute additional evidence to my view that *the dextrose-forming ferment enters the portal system by way of the splenic vein.*

THE FUNCTIONAL RELATIONSHIP BETWEEN THE PANCREAS AND SPLEEN.

The internal secretion of the pancreas and that of the spleen may perhaps be best studied by submitting to a careful analysis the hypothesis advanced by Schiff, sustained by

⁵ Minkowski: *Verhandl. d. XI Congr. für Inn. Medicin, Wiesbaden, 1892.*

⁶ Hédou: *Archives de Physiologie norm. et path.*, vol. iv, 1900.

Herzen,⁷ and defended by Lépine⁸ and others that the spleen supplies a ferment which, when added to pancreatic juice, greatly increases its digestive energy. Schiff believed that the splenic substance played an important part in the genesis of the pancreatic proteolytic ferment, but Herzen attributed to it the function of converting trypsinogen into trypsin, the albumin-solving constituent of the pancreatic juice. This subject was more recently studied experimentally by Gachet and Pâchon,⁹ who were led to conclude, as previously suggested by Laguesse (1893) and Schäfer (1895), that the spleen furnishes a true internal secretion which possesses a special affinity for the pancreas, the protrypsin of which it transforms into trypsin, as suggested by Herzen. This substance loses its properties at the boiling-point; is precipitated, when in aqueous solution, by alcohol; and is, therefore, of the nature of a ferment.

Lépine also confirmed Schiff's and Herzen's view by experiments *in vitro* and by blood-analyses. He found that a mixture of pancreas and spleen-pulp in glycerin possessed far more active properties than pancreas alone similarly prepared. On the other hand, the blood of an animal deprived of its spleen proved almost inert as a tryptic, while the blood of a normal dog possessed distinct digestive powers. Analysis of the experiments of these various authors distinctly indicates that some function of the kind mentioned exists. The anatomical relations of the organs involved, however, make it impossible for the internal secretion referred to to penetrate the circulation without first passing through the liver *with the blood of the splenic vein, which collects the pancreatic internal secretion and carries it to the portal vein.* This fact seems to suggest that, besides the amylolytic ferment, the portal carries a ferment to the liver calculated to insure the tryptic action upon albumins and kindred bodies. If we consider that we have in the blood of the portal channels all the products of digestion and that trypsin is "applied solely to albuminoid

⁷ Herzen: *Revue Générale des Sciences pures et appl.*, vol., 1895.

⁸ Lépine: *Société des Sciences Médicales de Lyon*, July, 1895.

⁹ Gachet and Pâchon: *Archives de Physiologie*, April, 1898.

conversions and changes" (Charles), the importance of the spleen's internal secretion will appear.

Albuminoids, especially those ingested with food, are not the inoffensive bodies that they appear to be; indeed, they constitute the foundation of some of the most dangerous substances that enter the organism when their molecular structure undergoes certain changes. Apart from any function of the spleen in the direction mentioned, the pancreatic trypsin supplied to the intestine—if we can judge by the manner in which a small remnant of pancreas will prevent glycosuria—must persist even when the pancreas is in a state of advanced disease. We saw that one-eleventh of the functional area of the adrenals sufficed to sustain the general oxidation processes. That the pancreas possesses at least four times more functional area than it absolutely needs has been experimentally demonstrated. With proper—fresh, uncontaminated—food, a normal organism is practically invulnerable, so splendidly is it armed against any chemico-physical decomposition that the ingesta may undergo. But these physiological defenses may be weakened through general or local adynamia, *i.e.*, lowered oxidation processes, and peptones, capable of yielding *toral-bumins*, *leucomaines*, *ptomaines*,—all albuminoids,—fail to undergo further splitting in the intestinal canal. Again, and under the same circumstances, notwithstanding the destructive action of the gastric and intestinal secretions, bacteria and their toxins may penetrate the debilitated villi and the portal circulation. The blood-stream, furthermore, may be invaded through peripheral organs not only by bacteria and their *toxins*, but also by *vegetable poisons* and venoms: all albuminoid substances, as previously emphasized. Even these do not represent all the sources of danger that a protective function, such as that represented by the pancreatic and splenic secretions, would have to meet, were they, as I believe, mainly intended to fulfill such a mission.

If toxic albuminoids reach the portal vein by way of the intestinal villi and the mesenteric veins, all conditions therein are most advantageous for the action which trypsin is known to exercise upon them: It acts with great energy in alkaline media, and the presence of oxygen does not inhibit its action;

if, therefore, the venous blood of the afferent channels should happen to contain an unusual amount of oxidizing substance through suprarenal overactivity, the tryptic disruption of peptones would not, to say the least, be prevented; in laboratory experiments the need of an antiseptic when pancreatic juice is used is well known; we have seen that, in the afferent vessels, the fluids derived from the intestines had been saturated therein with the antiseptic secretion of the glands of Brunner and Lieberkühn, and it is evident that their influence would normally continue in the venous channels; finally, the action of trypsin does not cease when the peptone stage is reached; it converts these into leucin, tyrosin, aspartic acid, etc., the fate of which derivatives I have traced down to urea, the end-product eliminated in the urine.

The rôle played by the spleen in the pancreatic digestion of proteids, and to which I add a prophylactic function, has been so ably reviewed by H. F. Bellamy in a comparatively recent number of the London *Lancet*¹⁰ that I will utilize the greater part of his paper to illustrate the various features that appear to me to furnish a solid foundation, not only for the views of Schiff and Herzen, but also for my own.

The author reviews the history of the question as follows: "Corvisart found that in dogs in full digestion there was for a certain time a constant rise to maximum in the digestive power of the pancreatic juice, succeeded by an equally constant fall to minimum. The maximum was attained during the eighth hour after the ingestion of a meal; the minimum from the thirteenth to the eighteenth hours. Meissner announced that in fasting animals the pancreatic juice possessed little or no peptonizing power. Schiff, after a number of experiments on such animals as rats, guinea-pigs, rabbits, and young dogs or dogs of small breed, found that during fast the pancreas really possessed almost no peptonizing power; the albumin imprisoned in the duodenum remained there for whole hours without dissolving, the infusion of the gland giving results equally negative. On the other hand, in the case of ravens and adult dogs of large breed the pancreas preserved during fast a certain digestive power, even in animals in a condition

¹⁰ H. F. Bellamy: London *Lancet*, Oct. 27, 1900.

of complete fast which had digested a copious meal the day before; under these circumstances, indeed, the infusion of the whole pancreas of a large dog was capable of digesting from 50 to 60 grammes of albumin. In such dogs this condition of weak digestion was maintained until toward the fourth hour after the meal, after which time digestion proceeded very much more rapidly, so that at the time of maximum the pancreatic infusion was capable of digesting from 50 to 60 grammes of albumin. As regard cats and small dogs, he was able to confirm the results of Corvisart. By these experiments, then, the above-mentioned observers succeeded in establishing the following two facts: (1) that the activity of the pancreatic juice or of an infusion of the gland is not continuous, but intermittent, and (2) that maximal activity appears regularly during the culmen of gastric digestion (from six to eight hours after a meal), at which time it is very considerable."

Passing now, for the moment, from the pancreas to the spleen, he proceeds briefly to examine the behavior of this organ in relation to digestive phases. "Lauret and Lassaigue in 1825 discovered that the spleen began to become congested at the moment when the stomach discharged chyle abundantly into the duodenum; that this is, however, merely a coincidence is shown by the fact that the congestion also occurs after ligature of the pylorus. Dobson in 1847 discovered that in a dog three hours after a meal the spleen is still as small and as anæmic as during fast; that it commences to dilate in the fourth hour after a meal; that five hours after it has attained its maximal turgescence, decreasing afterward from the seventh hour to attain toward the twelfth its minimal volume. Landois in the same year found that in the rabbit the relative weight of the spleen to the body-weight of the animal was the same two hours after a meal as after forty-eight hours of fast; that it increased considerably from the fifth hour, remaining high until the twelfth hour.

"The striking synchronism in the splenic congestion and the presence of trypsin in large quantity in the pancreatic juice or in an infusion of the gland was observed by Schiff and caused him to repeat all his former experiments on the tryptic digestion of albumins, this time on animals in which the spleen

had been for some time removed and on others in which it was prevented from dilating by ligature of its hilum at the time of the experiment. He experimented in this way upon a very large number of dogs and cats; nearly all his experiments were double: *i.e.*, performed at the same time and in the same manner on two animals selected so as to resemble one another as much as possible, and in only one of which had the spleen been extirpated or ligatured. These experiments were of two kinds: (1) those conducted with pancreatic infusions, and (2) those carried out in the living duodenum, the following being typical examples:—

“1. Infusions. Ligature of the Hilum of the Spleen.—Two cats, after fasting for 19 hours, received as much meat as they would eat; 1 hour afterward they were etherized, and the spleens, which were found to be in a state of contraction, were brought out through a wound in the abdomen and their hila were encircled by strong thread; in one of the animals the hilum was firmly tied, but in the other it was simply encircled and a knot was tied, leaving the splenic circulation perfectly free (this was done in the endeavor to equalize traumatic conditions as much as possible). The spleens were then replaced in the abdominal cavity and the wound was sutured. On recovering from the anæsthesia the animals did not appear to suffer. They were killed 6 hours later. Gastric digestion was found to be more advanced in the animal in which the splenic vessels were tied; the pancreas of both was cut up into small fragments and infused with 100 cubic centimeters of water for an hour at 35° C.; the liquid was afterward decanted and returned to the warm chamber together with cubes of albumin.

“Result.—In 7 hours the pancreatic infusion of the cat in which the hilum was not ligatured digested 17 grammes of albumin; that of the other did not digest at all even at the end of 12 hours.

“This experiment was performed on a large number of cats and dogs and always gave the same result. In spite, however, of the perfection of gastric digestion in the operated animals, it was possible to lay at the door of traumatism the absence of duodenal digestion; to correct this the experiment was repeated as follows:—

“Extirpation of the Spleen.—Two dogs—one normal, the other having undergone splenectomy a month previously, but at the time of the experiment in perfect health—were operated upon, while fasting, as follows: Etherization, ligature of the pylorus, injection into the stomach, per œsophagus laid bare and opened, of 50 grammes of peptone and 2 grammes of dextrin; to allow drainage of swallowed saliva the œsophagus was ligatured below the opening. Both animals were killed five hours later, and each pancreas was infused for three-fourths of an hour in 100 cubic centimeters of water at 35° C. Although death had occurred before the most favorable moment for the experiment,—i.e., in advance of the summit of the splenic curve,—the infusion coming from the dog with the spleen intact digested 17 grammes of albumin in 17 hours, while the other digested nothing even in 18 hours. Numerous experiments made in this manner always gave the same result. The spleenless dogs had in many cases undergone splenectomy several months before the experiment, and the determination in them of perfect conditions of health was always a matter of great care.

“II. Experiments in the Living Duodenum. Ligature of the Duodenum at Both Ends.—Two dogs after fasting for 17 hours received as much meat as they would eat and immediately afterward were operated upon as follows: Etherization, laparotomy, ligature of the pylorus and of the bile-duct, introduction into the duodenum of from 30 to 40 grammes of albumin, and ligature of the jejunal end. In one of the animals the splenic hilum was also ligatured. Both were killed 7 hours later.

“Result.—In the dog with the splenic hilum tied the albumin was found to be intact; it had, however, disappeared in the other.

“This experiment was also several times repeated on animals which had undergone splenectomy a long time previously, and always yielded the same result; it is, of course, capable of being combined with the preceding by making an infusion of the pancreas after the death of the animals. Such infusions give results in harmony with those furnished by the duodenum itself. Further, it will be remembered that in the pancreatic

juice of dogs of large breed Schiff generally found, even while fasting, a certain quantity of trypsin; when the same were spleenless, however, he was unable to find any.

"Digestion in the Normal Duodenum Provided with a Fistula.—A duodenal fistula was established in a dog. After complete recovery a measured and constant quantity of albumin was introduced every day into the duodenum inclosed in a small envelope of fibrous membrane fixed to the cannula by a thread some centimeters long. The progress of digestion was then observed, the following results being obtained: 1. When the animal was fasting the albumin took from 5 to 6 hours to become dissolved. 2. When the albumin was introduced into the duodenum during the 2 to 3 hours immediately following the ingestion of a meal by the animal it remained unchanged. 3. When introduced 4 hours after a meal it disappeared very quickly,—in about half the time, in fact, occupied during fast. These facts having been duly noted, the spleen was then extirpated, and after complete recovery the same experiment was repeated; very different results were now obtained. Whether fasting or in full digestion the time taken for the digestion of the albumin was exactly the same, viz.: from 5 to 6 hours. The acceleration in the peptonization which had formerly appeared after the fourth hour of digestion, and which coincided both with the appearance of trypsin in the pancreatic juice and with the dilation of the spleen, was now absent. The slow digestion (from 5 to 6 hours) in this experiment was probably entirely due to the secretion of the duodenal glands, which possess only a very feeble digestive power; the active, rapid digestion was due to the appearance, in large quantity, of trypsin in the pancreatic juice: a phenomenon wanting in the spleenless animal. . . . Schiff endeavored to interpret the facts by the following theory: During the congestion of the spleen a substance is produced within it which, carried away by the blood, gives to the pancreas the wherewithal to form its peptonizing ferment. . . . In 1872, however, the theory of Schiff received a rude shock through the great discovery of the zymogens by Heidenhain and his pupils. From the researches of this observer it appeared that, as the gastric mucous membrane forms at the

outset hardly any active pepsin, but a zymogen accumulating in its glands in the intervals of digestion, so the pancreas does not at once elaborate active trypsin but a substance destined to become trypsin under certain conditions and in a certain phase of the digestive act, this substance being, of course, the pancreatic zymogen trypsinogen, or protrypsin. The researches of Heidenhain are well known, and it suffices to recall here only one or more essential points: Thus from them we know that the pancreas of a fasting dog contains little or no trypsin, but merely trypsinogen; consequently its glycerin infusion possesses little or no digestive power; the infusion, however, of a dog in full digestion digests rapidly and copiously, because it contains trypsin. If the pancreas of a fasting dog be divided into two equal portions, one of which is infused at once and the other only after an exposure of 24 hours to the air, the first is found to be inactive, while the other is immediately and energetically active, from which it is clear that the inert trypsinogen which it contains becomes spontaneously transformed into active trypsin; indeed, it suffices to pass a current of oxygen through a pancreatic infusion, rich in trypsinogen and poor in trypsin (an active infusion), to transform it into an infusion possessing a digestive power. This transformation, then, is an oxidation, trypsin being oxidized trypsinogen.

"The fact observed by Heidenhain of the continuous formation and storing up of trypsinogen in the pancreas and its subsequent transformation into trypsin during the culmen of gastric digestion proved that the former substance at any rate enjoyed an origin quite independent of all influence outside the pancreas itself, and the hypothesis of Schiff as to the intervention of the spleen seemed, in consequence, to be at fault. But it was only the theory of Schiff which suffered by these new revelations; as far as the experimental results of the two observers were concerned, physiologists were face to face with two series of apparently contradictory facts—apparently because facts properly observed can never stand in contradiction with one another, and when they appear to do so it is merely because the interpretation of them is either false or incomplete. It fell to the lot of M. Herzen to unravel the tangled hypotheses. It appeared to him that, by modifying the hy-

pothesis of Schiff as to the manner in which the spleen acts as a tryptogene, a fusion of the respective facts of Schiff and Heidenhain could be brought about, and that, far from being antagonistic, they could be shown to be reciprocally corroborative. He argued thus: since the zymogen, even in splenectomized animals, is being continuously elaborated, and therefore independently of the spleen and its periodical congestion, and that it accumulates in the gland-cells during fast, but that it becomes rapidly and copiously transformed into trypsin only in the presence of the spleen and in direct proportion to its dilation, it would seem feasible that the spleen produces, by 'internal secretion' during its congestion, an unknown substance, which, carried away by the circulating blood, transforms the inert zymogen already deposited in the pancreas into active trypsin destined to pass into the secretion of the gland, and that the influence exercised upon the zymogen by this product of the spleen seemed to be a condition *sine qua non* for the transformation of the former into trypsin, at least in the living pancreas, since in the dead organ or its infusion it is so transformed by direct oxidation. This hypothesis of Herzen would seem to be further confirmed by the fact gleaned from the researches of both Schiff and Heidenhain, to wit: that the holding in zymogen of the pancreas at a given moment either of fast or digestion is always in inverse ratio to its holding in trypsin, and *vice versa*, while the latter is always in direct proportion to the spleen dilation.

"So far so good. But Herzen reasoned further. If the spleen really produces, during its congestion, a substance which brings about the transformation of the pancreatic zymogen into trypsin, it would then be possible to seize upon this substance in the spleen itself while in its turgescient condition (from 6 to 7 hours after a meal), and by at once making an infusion of it and mixing a certain quantity of this splenic infusion with pancreatic infusion made from the pancreas of a fasting animal (very rich in zymogen and very poor in trypsin, and consequently nearly inactive) there could be obtained *in vitro* a rapid and copious formation of trypsin easily recognizable by the amount of proteid digested in a given time. The control experiment would also be very simple, consisting merely

in mixing with the same pancreatic infusion that of a contracted and anæmic spleen, in order to observe whether it would have the same effect as that of the spleen dilated and engorged with blood. Artificial digestions actually carried out with these infusions gave enormous differences: whereas the pancreatic infusion alone, or that mixed with infusion of contracted spleen digested nothing or almost nothing, the same pancreatic infusion to which had been added infusion of engorged spleen digested rapidly and copiously; indeed, it had often completely digested its dose of proteid by the time that the other two, if digesting at all, had barely commenced. The mixed infusions thus behaved in the same way as a pancreatic infusion taken at the culmen of digestion.

"A large number of similar experiments were made with aqueous boric and glycerin infusions, each being double: *i.e.*, performed in two separate series of vessels, the one containing finely divided fibrin and the other equal-sized cubes of coagulated albumin. The results were always the same. . . .

"At the German Congress of Medicine held at Strasburg in 1886 Herzen exhibited several graduated flasks containing the residua of fibrin and albumin in a number of his digestions, the digesting liquid having been decanted and replaced by alcohol. The physiologists who examined them all recognized that the difference between the residua left by the pancreatic infusions alone and those of the mixture of the pancreatic and splenic infusions were very obvious. In a private conversation with Herzen, however, Heidenhain made the following criticism: It is well known that the pancreatic zymogen is very greedy of oxygen; on the other hand, the spleen during its dilation is engorged with blood. The splenic infusions exhibited were intensely colored by dissolved hæmoglobin—*ergo*, the undoubted and considerable acceleration in digestion obtained by adding such a liquid to another containing trypsinogen could be quite simply explained by the rapid oxidation of the zymogen at the expense of the hæmoglobin. This objection disconcerted Herzen in no inconsiderable degree, and he lost no time in making it the subject of experimental inquiry. He at length succeeded in disproving it by the following excellent experiment: The pancreas of a normal fasting dog

was infused in pure glycerin and the infusion was divided into eight equal portions. These eight portions were mixed with eight samples of blood received directly into a double volume of glycerin, of which four came from a fasting dog and four from a dog in full digestion with the spleen greatly dilated. The four samples were taken in both animals from (1) the femoral artery, (2) the femoral vein, (3) the splenic artery, and (4) a large splenic vein. The eight portions were then given the usual dose of fibrin and placed at a temperature of 40° C. Now, it is evident that the femoral and splenic arterial blood of the two animals contained more oxygen than their venous blood; the former, then, according to Heidenhain, should exercise a powerful influence on the digestion, equal in the two dogs. On the other hand, according to Herzen, the splenic venous blood alone should exercise this influence and especially that of the digesting animal. The result of the experiment was as follows: After one hour there was still no trace of digestion under the influence of the femoral blood, arterial or venous, nor of the splenic arterial blood of the fasting dog; first traces of digestion were beginning to manifest themselves under the influence of the splenic venous blood of this animal. Digestion was rather advanced in the case of the femoral arterial and venous blood and splenic arterial blood of the digesting dog; the fibrin had almost entirely disappeared under the influence of the splenic venous blood of the same animal.

“The answer could not be clearer: the product of the internal secretion of the spleen, borne therefrom by the circulating blood, is present during the period of the dilation of the spleen in feeble, but appreciable, quantity in the blood of the general circulation and abundantly in the splenic venous blood. The venous blood returning from the contracted spleen only contains it in very small quantities. This experiment, several times repeated, always gave the same result, showing that it is not the blood as such which favors the transformation of pancreatic zymogen into trypsin, but that, by picking up from the spleen the unknown substance possessing this property, the blood becomes its vehicle and means of communication with the pancreas.

"From the bulk of evidence collected by Herzen there thus seems to be very little room for doubt that, apart from hæmatopoietic, and possibly allied, functions possessed by the spleen, the organ furnishes a product of 'internal secretion' which causes in the pancreas the transformation of its inert zymogen into active trypsin."

Bellamy closes his article with a review of the criticisms to which the researches of Schiff and Herzen have been submitted. In the experiments of Lussana, in 1868, the spleens of three dogs were removed and the animals were subsequently killed to ascertain whether the extract of their pancreas would digest coagulated albumin. The pancreatic infusion of the glands of two of the dogs digested 0.25 gramme of albumin in 24 hours; that of the third digested 1.10 grammes in the same period of time. "The latter animal had, however, been killed three hours after a meal: *i.e.*, at a moment when, even had it been in possession of its spleen, that organ would not yet have commenced to become congested. The experiment, therefore, gave the result which might be expected,—*viz.*: no digestion,—for nobody would accept seriously the digestion of 1.10 grammes, knowing that the pancreas of a dog when digesting can dissolve from 50 to 60 grammes of albumin. . . ." Indeed, the experiments of Lussana appear to us to be confirmatory of Schiff's and Herzen's views.

Carvallo and Pachon also reported negatively, but, errors in their experimental procedures having been brought to their attention by Herzen, subsequent experiments caused Pachon and a new collaborator, Gachet, to reach the conclusions sustaining the views of Schiff and Herzen to which we have referred on page 368. "Nay, they did more," says Bellamy; "they invented an entirely new experiment, at once original and ingenious, which consisted in realizing *in vivo* what Herzen had hitherto only done *in vitro*. This experiment was as follows: A dog, which a long time previously had undergone splenectomy, was anæsthetized and half its pancreas was removed and immediately infused; at the same time a normal dog, in the height of digestion, was killed and its congested spleen was infused in water, and this infusion was injected into the venous system of the spleenless dog; from 15 to 20

minutes afterward the remaining half of the pancreas of the latter dog was infused exactly like the first; of the two infusions when given fibrin and albumin, the second only digested rapidly and copiously."

The investigations of Popelski are next reviewed. "In both normal and splenectomized cats," says Bellamy, "he collected the pancreatic juice by means of a cannula introduced into the duct of the gland, and was unable to find any difference in digestive activity. As, however, his cats had been fasting since the day before, his experiments were made outside the digestive period during which the spleen, becoming congested, furnishes abundantly its product of internal secretion which transforms rapidly and copiously the zymogen into trypsin." . . . "But Popelski also performed some analogous experiments on a dog with a permanent pancreatic fistula, made according to the method of Pawloff. The pancreatic juice of this animal was several times collected and examined before and after splenectomy without any difference in activity being demonstrable. This result, however, elicits no surprise in view of the fact that in both instances the juice was always collected immediately after a meal—*i.e.*,—again to repeat it—in advance of that digestive period during which the spleen enters into function and the pancreas abounds in trypsin; so that as well in this experiment as in that with his cats, Popelski was placed in that position in which the presence or absence of the spleen was a matter of perfect indifference. . . ." The discussion of the various features in point have led to considerable acrimony, but the impartial observer cannot fail to consider that the position of Herzen, of those reviewed, is the only tenable one.

In an article written since Bellamy's review was published Popelski¹ reiterates his views, and states that since it has been demonstrated that there exist in the organism *bodies in the nature of ferments possessing oxidizing properties*, which he believes to be derived mainly from leucocytes, the results obtained by Schiff, Herzen, Pachon and Gachet can all be explained by their action. During the height of digestion

¹ Popelski: *Vratch*, Feb. 3, 1901.

digestive leucocytosis prevails, and, an accompanying destruction of these cells yielding more oxidizing bodies, the latter, he thinks, are the source of conversion of protrypsin or trypsinogen into trypsin, which thus becomes a function of the blood. Thus, the spleen would have nothing to do with the process, the hyperemia and dilation of this organ during the formation of trypsin being regarded merely as concomitant phenomena.

The only feature of interest to us in Popelski's last paper is the fact that his experiments were performed in accordance with the directions of Schiff. That he should be driven thereby to ascribe all the phenomena witnessed to the action of "oxidizing bodies" adds materially to the data contributed by Schmiedeberg, Jaquet, Abelous and Biarnés, and Salkowski, proving experimentally the existence of an oxidizing substance, and is suggestive. Indeed, when, in addition to this, we realize the strength of Heidenhain's position, the manner in which it shook to its very foundation the equally strong position of Schiff's views as developed by Herzen, by pointing to *the influence of oxygen* as another agency through which trypsin could be developed from trypsinogen, "trypsin being oxidized trypsinogen," the following query suggests itself: Are we not dealing with two processes working in sequence, a part of the trypsinogen secreted in the splenic vein being converted by the splenic secretion for use in the portal vein, and the rest being converted, when the arteries are reached, by the oxidizing substance?

To determine whether such a deduction is at all warranted or whether it is subject to modifications through which the various views submitted and our own can be conciliated, we find it necessary to closely analyze the manner in which the pancreas and the spleen are functionally governed.

THE FUNCTIONAL MECHANISM OF THE PANCREAS.—The pancreas will first receive our attention. Referring to this organ, Howell says: "Until recently little direct evidence had been obtained of the existence of secretory nerves. Stimulation of the medulla was known to increase the flow of pancreatic juice and to alter its composition as regards the organic constituents, but direct stimulation of the vagus and the sympathetic

nerves gave only negative results. Lately, however, Pawlow and some of his students have been able to overcome the technical difficulties in the way, and have given what seems to be perfectly satisfactory proof of the existence of distinct secretory fibers comparable in their nature to those described for the salivary glands. The results that they have obtained may be briefly stated as follows: Stimulation of either the vagus nerve or the sympathetic causes, after a considerable latent period, a marked flow of pancreatic secretion. The failure of other experimenters to get this result was due apparently to the sensitiveness of the gland to variations in its blood-supply.¹² Either direct or reflex vasoconstriction of the pancreas prevents the action of the secretory nerves upon it. Thus, stimulation of the sympathetic gives usually no effect upon the secretion, because vasoconstrictor fibers are stimulated at the same time; but if the sympathetic nerve is cut five or six days previously, so as to give the vasoconstrictor fibers time to degenerate, stimulation will cause, after a long latent period, a distinct secretion of the pancreatic juice."

The quotation almost suffices to show that the sympathetic fibers are vasoconstrictors as elsewhere, in the light of our views, and that the secretory nerve is the vagus. This view is conclusively supported, however, by evidence from other directions. As to the vagus, François-Franck and Hallion¹³ in addition to the dilator effects produced on the liver state that "this vasodilator action is also found in the pancreas." Stimulation of the peripheral ends of both vagi, after section, between the cardiac plexus and the diaphragm caused a wide dilation of the pancreatic vessels, which persisted some time, entailing a lowering of the aortic pressure. They also obtained dilation of these vessels reflexly, by stimulating the central end of the nerve after it had been cut on a level with the œsophagus. We have also in the experiments of Mette¹⁴ and Kudrewetzky¹⁵ evidence of the direct action of vagal stimuli upon muscular fiber. Having observed that the secretion caused by stimulating

¹² All italics are our own.

¹³ François-Franck and Hallion: *Loc. cit.*

¹⁴ Mette: *Archiv f. Physiol., Suppl. Bd., 1894.*

¹⁵ Kudrewetzky: *Ibid.*

one vagus could often be arrested by exciting the other vagus, he concluded that this nerve contained antagonistic fibers. This dual set becomes unnecessary, however, if stricto-dilation is accepted as the mechanism of the vasodilation observed by François-Franck and Hallion. Indeed, vagal stimuli capable of causing contraction of the vascular *muscles* to which stricto-dilation is due, can as well induce contraction of the muscular coats of Wirsung's duct, and thus arrest the flow of secretion of pancreatic juice precisely as it does that of bile.

As the sympathetic supply François-Franck and Hallion¹⁶ obtained plethysmographically vasoconstrictor effects on stimulating the splanchnic, and traced the constrictor fibers to the cord. The fibers were supplied through the fifth thoracic communicating branches to the second lumbar inclusive, the majority of them reaching the solar plexus by way of the greater splanchnic. The fibers then formed, they contend, "a secondary plexus enveloping the pancreatic artery." They also state that "this arterial path seems to be the only one, since the destruction of the fibers that accompany the artery suppress the pancreatic vasoconstrictor effects of any sympathetic branch stimulated." Again, Popelski¹⁷ refers to various ways in which inhibition of the flow of secretion may be caused. Among these are: Stimulation of the vasoconstrictor fibers, and stimulation of "secretion-inhibiting" fibers supposed by him to represent a special set. The mode of termination of the sympathetic fibers on the pancreatic artery as given by François-Franck and Hallion readily accounts for the inhibition caused by excessive excitation of the nerves. These (sympathetic) fibers are thus evolved from the suppositious special "secretion-inhibiting" nerves—a rather incongruous combination, since by arresting the flow of blood to the organ, they prevent and may arrest the secretory process.

It is evident that these vasoconstrictor fibers are distinct from the true secretory fibers, for Pawlow¹⁸ says, alluding to Popelski's work: "By a careful preparation of the nerves,

¹⁶ François-Franck and Hallion: *Archives de physiol. norm. et pathol.*, T. ix, p. 661, 1897.

¹⁷ Popelski: *Centralbl. f. Physiol.*, Bd. x, S. 405, 1896.

¹⁸ Pawlow: "The Work of the Digestive Glands," *Eng. Trans.*, London, 1902.

some branches were discovered whose excitation caused a secretion without any latent period almost as promptly as the chorda expels saliva. From the latter fact we must conclude that in the branches mentioned, the secretory fibers of the pancreas have been anatomically separated from the inhibitory." Finally, a proof that we are dealing with exaggerated constriction ending in experimental inhibition and not with a true secretory nerve is afforded by the following observation of Kudrewetzki's¹⁹: "If the sympathetic nerve be excited by means of an induced current, a gentle intermittent advance of the secretion is observed, but only during the first few seconds; during the later stages of the excitation, and after its stoppage, the secretion is completely arrested." We have here, obviously, the identical result observed in the submaxillary gland when the cervical sympathetic is stimulated—a brief exacerbation of activity due to the propulsion of a small quantity of blood into the secretory elements—and simultaneously additional evidence that the sympathetic in the pancreas fulfills vasoconstrictor functions.

This involves the conclusion that as elsewhere the blood-plasma—laden with oxidizing substance—is able to reach the glandular cells. This is shown by a brief review of the relationship between the nervous and vascular structures of the organ.

Referring to the blood-vessels, Piersol says: "The larger arterial branches run within the interlobular connective tissue, sending off vessels which pass between the lobules and supply the glandular parenchyma with twigs. These latter enter the lobules and form *net-works which inclose the individual acini within the capillary reticulum*. The capillaries lie beneath the basement membrane in close relation with the glandular epithelium. The veins accompany the arterial trunks within the connective tissue." A similar arrangement prevails in the distribution of the nerve-terminals. According to Ramón y Cajal and C. Sala, the pancreas contains many nerve-cells and fibers of Remak. Some cells are found in the interacinous spaces; others are in contact with the intrinsic vascular walls, and *their finer prolongations surround the glandular cells*.

¹⁹ Kudrewetzki: Quoted by Pawlow: *Loc. cit.*

Those connected with the vessels *form a plexus around them*, and send extremely fine filaments to the muscular elements. Alluding to the nerve-cells, Ramón y Cajal says: "We may consider this cell as a special cell, all the prolongations, or almost all the prolongations, of which possess the meaning of nervous prolongations *contrary to the cells of the sympathetic chain*, that have two kinds of prolongations: along one, or fiber of Remak, for the viscera, and short prolongations comparable to the protoplasmic prolongations of cerebro-spinal cells, destined to establish relations by contact between the neighboring cells of a ganglion." Berdal, who quotes the above, therefore recognizes two varieties of nerve-fiber in the pancreas: "1. The nerve-fibers formed by the cellular prolongations and which supply the periacinous and perivascular plexuses. 2. The nerve-fibers derived from the sympathetic nerves which penetrate into the pancreas *with the vessels*."

On the whole the functions of the pancreas appear to be governed as follows:—

1. *The nervous supply of the pancreas is derived from the vagus and the sympathetic systems.*

2. *When the secretory functions of the organ are to be enhanced, the vagal terminals cause vasodilation of its arterioles, thus increasing the arterial blood circulating through it.*

3. *When the functional activity of the pancreas is to be diminished its arterioles are caused to contract by the sympathetic nerves, and the blood circulating through the organ is reduced.*

FUNCTIONAL MECHANISM OF THE SPLEEN.—The innervation of the spleen includes, as a predominating feature, the distribution of a fair proportion of the terminal fibers to the muscular elements, which, in man, are mainly supplied to the trabeculæ. "We have evidence," says Professor Foster, "that the muscular activity of the spleen, whether of the muscular capsule and trabeculæ and arteries combined, or of the latter alone, is under the dominion of the nervous system. *A rapid contraction of the spleen may be brought about in a direct manner by stimulation of the splanchnic or vagus nerves.*" . . . "it may also be caused by stimulation of the *medulla oblongata* with a galvanic current or by means of *asphyxia*. Though the

matter has not yet been fully worked out, we have already sufficiently clear indications that the flow of blood through the spleen is, through the agency of the nervous system, varied to meet changing needs. At one time a small quantity of blood is passing through or is being held by the organ and the metabolic changes which it undergoes in the transit are comparatively slight. At another time a larger quantity of blood enters the organ and is let loose, so to speak, into the splenic pulp, there to undergo more profound changes, and afterward to be ejected by rhythmic contractions of the muscular trabeculæ."

That rapid contraction of the spleen should occur under stimulation of the splanchnic nerve is easily accounted for when the rôle of sympathetic nerves—those it supplies the organ—is considered to be that I have attributed to them in the foregoing chapters: that of vasoconstrictor. Indeed, it is plain that under stimulation these nerves should reduce the caliber of the arterioles, and, therefore, the volume of blood admitted into the organ, and that it should contract rapidly owing to continued depletion of its veins. The constrictive effect of stimulation of the medulla on the arteries we have repeatedly seen; as this is due to contraction of their muscular coats, the spleen is evidently influenced in a manner similar to that following stimulation of the splanchnic, the smallest arteries being the first obstructed under violent vasoconstriction.

But why should stimulation of the vagus also induce splenic contraction? This requires an examination of the distribution of the nerve-terminals. The innervation of the spleen was studied by Kölliker in various animals,²⁰ and his observations, when viewed in the light of my conception of the functional mechanism of glandular organs, are suggestive. "The vasomotor nerves enter the organ with the large arteries. In the *walls* of the large arteries the main trunks form a well-marked superficial *plexus* with oblong meshes in the adventitia, and a *deep*, more quadrate *net-work* in the tunica media; some end in the little branched arborizations in this coat. The smaller arteries and the trabeculæ receive their nerves from

²⁰ Kölliker: Sitzungsbericht d. Würsb. Phys. med. Gesellschaft, No. 2, 1893.

the rich maze of fibers in the pulp, consisting of axis-cylinders, which, however, do not anastomose. Other fibers form a plexus on the surface of the trabeculæ, and from this fibrils penetrate into the interior of the trabeculæ (*which contain much smooth muscle*) and end by free arborizations." Free terminals, which Kölliker regards as sensory fibers, were also found. When we consider that the trabeculæ penetrate deeply into the interior of the organ from the inner surface of the capsule in every direction, thus forming a spongy frame-work, and that the muscular capsule overlying the organ and this spongy frame-work, is also supplied with vagal nerves, its contraction under the influence of the latter under stimulation also becomes self-evident in the light of our views: The vagus acting as a vasodilator allows an excess of blood to penetrate into the muscular elements, causing them to contract and thus to diminish the size of the organ. Indeed Roy²¹ who first called attention to the rhythmic contractions of the spleen, ascribed them to impulses received by way of the vagus.

A feature of the experimental work upon this organ which tends greatly to produce confusion in the interpretation of its function, is the belief that it is supplied with inhibitory fibers. Thus, according to Schäfer²² these fibers are contained in the splanchnic nerves and their stimulation "produces a dilatation of the spleen." It is plain, in the light of our interpretation of "inhibition," that we are merely dealing with an experimental phenomenon due to the excessive vasoconstriction which electricity produces when applied to sympathetic vasoconstrictors, and that the organ does not receive "inhibitory fibers" as textbooks call them.

The interpretation of the splenic functional mechanism in accordance with our views is greatly facilitated when the microscopical anatomy of the organ is considered in the light of F. P. Mall's²³ researches. The organ is divided, as is the liver, into lobules, each of which is bounded by "interlobular" trabeculæ: those to which we have already referred. Each

²¹ Roy: *Journal of Physiol.*, vol. III, p. 203, 1880-2.

²² Schäfer: "Proceedings of Royal Society," London, 1896, vol. IIx, No. 365; and *Journal of Physiology*, 1896, vol. xx.

²³ F. P. Mall: *Johns Hopkins Hospital Bulletin*, Sept., Oct., 1898.

lobule is about 1 millimeter in diameter, is partitioned into about ten compartments by intralobular trabeculæ, and receives an artery which sends minute branches to each compartment. There is also considerable analogy between each one of these compartments and the hepatic lobule, the hepatic cells being represented by masses of pulp separated by venules, which vessels carry back to the veins leading to the greater splenic vein the various elements transferred to the liver. The pulp itself is made up of an extremely delicate reticulum, in which are found red corpuscles, lymphocytes, remains of corpuscles with or without pigment, etc. The arteries—which bring to the organ oxidizing substance—soon after entering the organ assume an unusual shape: their outer coat becomes lymphoid, forming nodules similar to the solitary follicles of the intestine,—i.e., the Malpighian corpuscles,—in which lymphocytes are formed. When, after numerous subdivisions, their diameter becomes greatly reduced, the arteries resume their normal adventitia and on reaching the pulp in the compartments break up into minute capillaries. The arrangement is, after all, an uncomplicated one, and similar, in general plan, to that of other organs reviewed.

The connection between the nervous supply of the spleen and that of the other digestive organs becomes evident when the distribution of the celiac-plexus branches is recalled. "The splenic plexus," say Pick and Howden,²⁴ "is formed by branches from the celiac plexus, the left semilunar ganglia, and from the right pneumogastric nerve. It accompanies the splenic artery and its branches to the substance of the spleen, giving off, in its course, filaments to the pancreas (pancreatic plexus) and the left gastro-epiploic plexus, which accompanies the gastro-epiploica sinistra artery along the convex border of the stomach." If we append to this Kölliker's description of the intrinsic nervous supply and the manner in which it is connected with the blood-vessels, it will become apparent that we have a counterpart of the vasculo-nervous mechanism of all the other organs of the digestive system we have studied, viz., a system of vagal fibers capable of inciting the spleen to

²⁴ Pick and Howden: "Gray's Anatomy," p. 806.

increased functional activity by causing an excess of blood to enter the organ, and sympathetic fibers to reduce its functional activity by causing the vessels to resume their normal caliber.

The functions of the Malpighian corpuscles around the vessels would thus be insured by fibers from the vagus. Indeed, Fusari²⁵ traced nervous filaments within these bodies. The pulp is also possessed of a "rich maze of fibers consisting of axis-cylinders"—doubtless sensory structures. But here an independent motor supply must also be present, since we also have fibers that form "a plexus on the surface of the trabeculae," filaments from which penetrate *into* the trabeculae. These, we have seen, contain much smooth muscle, and the nerve-filaments are connected with them by "swellings" (Fusari), evidently end-plates. Kupffer's bile-alveolus, with its canaliculi, is recalled by a similar receptacle: *i.e.*, Mall's "intralobular venous spaces," which form the starting-point of the venules that ultimately end in the large trunks leading to the splenic vein.

On the whole, we may conclude as follows:—

1. *The nerves of the spleen are derived from two autonomous sources, the vagus, or pneumogastric, and the sympathetic system.*

2. *The functional activity of the spleen is incited by the vagal nerves distributed to its arterioles: by causing dilation of these vessels, they admit an excess of blood into all the structures of the organ, causing the latter to dilate.*

The vasoconstrictor functions of the sympathetic are as evident here as in other organs studied. "The spleen," says Howell, "is supplied richly with nerve-fibers which, when stimulated either directly or reflexly cause the organ to diminish in size. According to Schäfer these fibers are contained in the splanchnic nerves, which carry also inhibitory fibers whose stimulation produces a dilatation of the spleen." The sympathetic supply of the spleen has been clearly shown. Bulgak^{26a} obtained vasoconstrictor effects, the organ becoming pale and shrunken, by stimulating fibers which he traced to the semi-lunar ganglion and thence to the left splanchnic. Tarchanoff

²⁵ Fusari: *Archives Italiennes de Biologie*, Turin, vol. xix, p. 238, 1894.

^{26a} Bulgak: *Virchow's Archiv*, Bd. lxxix, p. 181, 1877.

reached similar results but by stimulating either splanchnic. Schäfer and Moore studied the same subject by means of a plethysmograph specially constructed to avoid any obstruction to the circulation in the organ's extrinsic vessels. They found the spleen extremely responsive to blood-pressure fluctuations, and obtained constriction by stimulating either splanchnic, the left, however, giving more marked results than the right. The constrictor fibers were found to arise from the third thoracic to the first lumbar inclusive, the most active arising from the sixth, seventh, and eighth thoracic. This evidence clearly shows that the rôle of the spleen's sympathetic supply is purely vaso-constrictor. Hence:—

3. *When the functional activity of the organ is to be diminished, the sympathetic fibers cause constriction of the arterioles, thus reducing the volume of blood admitted into the organ and passive contraction of its capsule.*

The rôle of the spleen has not been so far clearly established. Howell, in the second edition of his text-book (1907) writes in this connection: "As to the theories of the splenic functions, the following may be mentioned: 1. The spleen has been supposed to give rise to new red corpuscles. This it undoubtedly does during foetal life and shortly after birth, and in some animals throughout life, but there is no reliable evidence that the function is retained in adult life in man or in most of the mammals. 2. It has been supposed to be an organ for the destruction of red corpuscles. This view is founded chiefly on microscopical evidence according to which certain large amœboid cells in the spleen ingest and destroy the old red corpuscles, and partly upon the fact that the spleen tissue seems to be rich in an iron-containing compound. This theory cannot be considered at present as satisfactorily demonstrated. 3. It has been suggested that the spleen is concerned in the production of uric acid. This substance is found in the spleen, as stated above, and it was shown by Horbaczewsky that the spleen contains substances from which uric acid or xanthin may readily be formed by the action of the spleen-tissue itself. More recent investigations²⁶ have shown that the spleen, like the liver

²⁶ Consult Jones and Austrian: *Zeit. f. physiol. Chem.*, Bd. xlviii, S. 110, 1906.

and some other organs, contains special enzymes (adenase, guanase, and xanthin oxydase), by whose action the split products of the nucleins may be converted to uric acid, and it is probable, therefore, that this latter substance is constantly formed in the spleen. 4. Lastly, a theory has been supported by Schiff and Herzen, according to which the spleen produces something (an enzyme) which, when carried in the blood to the pancreas, acts upon the trypsinogen contained in this gland, converting it into trypsin." The latter is treated at length under the next heading.

The statement that the spleen contains, as do other organs, such ferments as adenase, guanase, and xanthin oxydase is suggestive, in view of the fact that they are all oxidizing ferments. This fact is all the more interesting in that, as shown below, it is the plasma alone, *i.e.*, plasma deprived of its red corpuscles which circulates in the intercellular spaces of the pulp-cords.

An incidental remark of Professor Mall's, in the contribution previously referred to, goes far toward demonstrating that I have not erred so far in ascribing to the blood-plasma *per se* the active part in the blood's function. This constitutes such a far-reaching feature of this entire work that the following lines appear to us as timely: "The microscopical anatomy shows that the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease and granules only with difficulty. In life *the plasma* constantly flows through the *intercellular spaces* of the pulp-cords, while the *blood-corpuscles keep within fixed channels*. Numerous physiological experiments which I have made corroborate this view." If this can occur in the spleen it is doubtless possible elsewhere in the organism, especially when we consider that red corpuscles average in diameter about $\frac{1}{3,000}$ of an inch, while the lumen of the majority of functional capillaries is less than one-half that size. Of course, corpuscles adjust themselves to the dimensions of the structures surround them; but it is apparent that in many instances—the tortuous capillaries of pericellular net-works, for instance—such a system could but compromise the free circulation of the fluids, and, simultaneously, the functional efficiency of the organ itself.

THE SPLENO-PANCREATIC INTERNAL SECRETION.

From the data already submitted as to the functions of, and the functional relationship between the spleen and pancreas, it is evident that each possesses its own complete mechanism, and that *in both organs, as elsewhere in the economy, the oxidizing substance (adrenoxidase) or the blood containing it is the source of functional activity.*

Still, have we any reason to believe, with Popelski, that it is through oxidation that the intrapancreatic trypsinogen becomes converted into trypsin? Can we say, for instance: the intrapancreatic conversion of trypsinogen into trypsin is not effected by the splenic ferment, but by the oxidizing substance, when the efferent vagus nerves transmit appropriate impulses? We think not, much as such a process would coincide with the multiple functions that we have already ascribed to the oxidizing substance.

We have seen that when the pancreas becomes functionally active its arterioles are caused to dilate by their vagal nerve terminals, and that the speed of the blood-flow through the organ is increased. Yet, while the net-work of capillaries is very rich, these *encircle* the secreting lobules, and, though in close relation with the glandular epithelium beneath the basement membrane, they in no way, as in the spleen, break up into reticulated tissue wherein their blood is poured; they merely lapse, as elsewhere in the organism, into venules, which ultimately carry the blood to the larger venous channels. Blood and trypsinogen do not come into contact, therefore, in the ducts of the typical pancreatic lobule: that which textbooks employ to illustrate the origin, centripetal migration, and functional elimination of the zymogen granules. These are lost in the lobular lumina and ultimately reach the greater duct on its way to the intestine, without apparently having come into contact with the oxidizing substance.

But, this being the case, how can we account for the experimental evidence adduced by Schiff and Herzen and other physiologists who have confirmed their work? How can we explain, for instance, the digestion of 17 grammes of albumin in 7 hours with pancreas obtained from a normal cat and *no*

digestion in 12 hours with pancreas from one in which the vessels of the splenic hilum had been ligated: an experiment repeated many times, and always with identical results?

It is evident that, if—as believed by Schiff and Herzen—the circulatory cycle must be traversed by the splenic ferment before the pancreas can be influenced by it, this ferment will merely pass *through* the pancreas without in any way converting trypsinogen into trypsin, and fruitlessly re-enter the splenic venous current. There being no connection between bloodstream and trypsinogen and none between the latter and the splenic ferment, we are now reduced to either deny the need of any converting agency, and simultaneously close our eyes to all the experimental data adduced,—including Popelski's, which sustain the existence of *some* process which has imposed the necessity upon him of accounting for *results* witnessed,—or seek elsewhere for an explanation of the phenomena recorded. Thanks especially to the labors of Langerhans,²⁷ Laguesse,²⁸ and Opie,²⁹ this task will be greatly facilitated.

Laguesse having studied the islands of Langerhans in the pancreas of an adult man (an executed criminal) and of a child which has died several hours after birth without having taken nourishment, and in the sheep, reached the following deduction, quoted from one of our own reviews of his work.³⁰ “Long before the pancreas begins its function as a digestive gland granules of secretion accumulate in the internal zones of the cells; and, when these come *into contact with the blood*, a portion of them appear as though dissolved, while in others the granules are resorbed. It might be supposed, with some reservations, that an internal secretion always exists in the cell,—very much developed, however, and preceding the external secretion in the fœtus. Later, each cellular group would be first full, then acinous, furnishing alternately an internal and an external secretion.” Opie refers to the observations of Kühne and Lea³¹ in injected specimens, in which these in-

²⁷ Langerhans: Inaugural Dissertation, Berlin, 1869.

²⁸ Laguesse: Comptes-Rendus Hebdom. des séances et mémoires de la Société de biologie, Paris, No. 28, 1893.

²⁹ Opie: Johns Hopkins Hospital Bulletin, Sept., 1900.

³⁰ Laguesse: “Annual of the Universal Medical Sciences,” vol. v, 1894.

³¹ Kühne and Lea: Untersuch. a. d. Physiol. Inst. d. Univ. Heidelberg, II,

vestigators "found scattered through the organ glomerular structures composed of dilated and tortuous capillaries, and showed that these glomeruli correspond to the cell-groups which Langerhans described. The islands are penetrated by numerous wide, tortuous capillaries, which lie between cells, forming irregular, anastomosing columns. Material injected into the *duct* of the gland does not penetrate the islands." The view that the islands of Langerhans furnish an internal secretion is indirectly sustained, and the histological topography outlined seems to furnish a clue to the mechanism involved: *i.e., the existence of two sets of glands capable of yielding similar products, but adjusted individually, as regards distribution, to the needs of two systems: the digestive system and the circulatory system.*

To develop this proposition and that on page 379, we will employ the excellent paper of E. L. Opie,³² in which the entire subject is not only reviewed, but also greatly elucidated through personal investigations. The quotations from his article will be limited, however, to the features bearing directly or indirectly upon the question in point, as given in the above italicized lines:—

"Schäfer and Diamare think that the vascular islets probably furnish an internal secretion. The only evidence in support of this suggestion is contained in the short preliminary notice of Ssobolew. He states that after feeding animals on carbohydrates the cells of the islands become more granular. After ligating the duct of Wirsung in dogs, the islands of Langerhans, he finds, are not involved in the sclerotic process which follows. He thinks that this fact explains the absence of glycosuria after ligation of the pancreatic ducts. In human cases I had observed after duct obstruction similar resistance of the islands to the consequent inflammation. In pancreases of two diabetics Ssobolew was unable to discover islands of Langerhans.

"In the human pancreas the islands were found to be more numerous in the splenic end, or tail, than elsewhere. To obtain a numerical statement of their relative abundance, their

³² E. L. Opie: *Loc. cit.*

number was determined in a sectional area of 0.5 square centimeter. Sections about 10 millimeters thick were made from the enlarged duodenal portion of the pancreas, or the head; from the midportion, or body; and from the splenic end, or tail. The following table gives their number in an area of 0.5 square centimeter in sections taken from the head, body, and tail of ten normal organs:—

TABLE I.

	HEAD.	BODY.	TAIL.
I.....	14.0	13.0	30.0
II.....	39.0	25.0	42.0
III.....	4.0	4.0	19.0
IV.....	4.0	10.0	43.0
V.....	27.0	18.0	59.0
VI.....	25.0	27.0	26.0
VII.....	18.0	18.0	29.0
VIII.....	6.0	10.0	29.0
IX.....	44.0	32.0	61.0
X.....	14.0	23.0	32.0
Average.....	18.3	18.0	34.0

“The table shows that the islands are more abundant in the tail, or splenic end, than in the head and in the body, where they are present in approximately equal number. They are almost twice as numerous in sections from the tail as in those from other parts. Since the number in only one plane is recorded, in order to obtain their actual relative abundance it is necessary to square these figures. They are then found to be slightly less than three and a half times as numerous in the tail as elsewhere.

“The cells composing the islands resemble those of the acini. They have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body. The basal zone of the secreting cell, as is well known, stains deeply with nuclear dyes,—for example, hæmatoxylin or methylene blue,—while the central portion, which contains zymogen granules, remains unstained. The cells of the island, however, do not stain with nuclear dyes, while with eosin their protoplasm takes a homogeneous bright-pink color. The nuclei differ but little from

those of neighboring acini. They vary considerably in size, and not infrequently one finds very large, round, vesicular nuclei whose diameter is two or more times that of those about. Occasionally the cells, forming columns between which are the anastomosing capillaries, are very closely packed together, and nuclei are situated almost side by side; more frequently the cells of the island are less numerous and the nuclei are less closely crowded together.

"The outline of the island is usually round or oval, and is not infrequently accentuated by a delicate circle of fibrous tissue. In other instances the outline is less sharp, and the body accommodates its shape to that of the neighboring acini. Occasionally one sees, apparently within the island, cells arranged, as in the acini, about a central lumen, and, indeed, in many instances it is difficult to convince one's self that they do not form part of it. The impression is produced that the columns of the island are in continuity with cells having an acinar arrangement. Since the islands and the secreting acini have a common origin, it is not inconceivable that they may occasionally remain continuous in the adult organ. When the fetal pancreas is affected by congenital syphilis, the islands, I have found, retain their continuity with the secreting structures.

"In the human pancreas the groups of acini about terminal ducts are not sharply defined by connective tissue; so that individual lobules, as in the human liver, are indistinctly marked off and in places apparently fuse with one another. In the pancreas of the cat the lobules, like those in the liver of the pig, are much more sharply outlined by interstitial tissue. Details of structure have been studied in the pancreas of the cat.

"The parenchyma is divided by septa of fibrous tissue into small polygonal areas in size and shape. When injected with Berlin blue, a small ramification of the ducts is found to penetrate the isolated group of acini. These subdivisions, or lobules, often appear completely isolated by fibrous tissue from those near by, but when one of them is traced through a series of sections its separation may be uniform, and in places one finds the parenchyma of adjacent lobules in contact, the

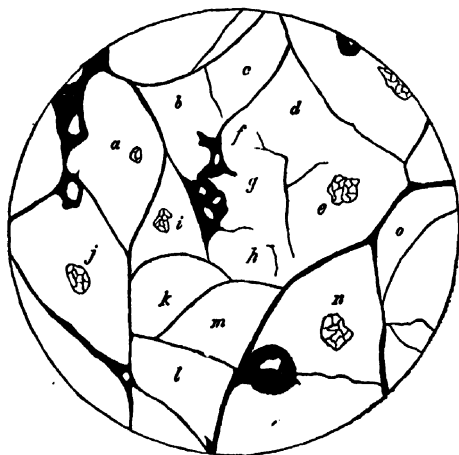
dividing septa being incomplete. That these polygonal structures are actually independent of one another and represent units of structure is readily demonstrated by causing an inflammatory increase of the interstitial tissue. If the pancreatic ducts of a cat are ligated and the animal killed at the end of two or three weeks, the gland is found to be the seat of a chronic interstitial inflammation, characterized by an increase of the interlobular tissue. The lobules are completely separated from one another by narrow bands of firm, fibrous tissue, and occur in sections as rounded, triangular, or polygonal areas of parenchyma.

"The islands of Langerhans occupy a position near the center of the lobule, and in the splenic end of the gland each lobule contains an island. In a given section many lobules whose limits are more or less distinctly outlined are seen to contain islands situated near their center, while in neighboring lobules such structures may not be discoverable. If, however, serial sections are studied, every lobule is found to contain an island. Its presence within the lobule is not constant in other parts of the organ, and in the extremity of the descending arm of the gland they are very few in number.

"The lobules are grouped about the medium-sized ducts. The main ducts give off branches approximately at right angles to their course. Branching one or more times, a duct forms the center of a group of lobules, which is usually elongated in form and tapers to a point at or near the surface of the gland. Such lobule groups are separated from one another by relatively wide bands of areolar tissue much looser in texture than that separating the individual lobules. The lobule groups in the fresh state or in tissue macerated a few days in Muller's fluid may be separated from one another by careful teasing. In the loose tissue lie the larger ducts, arteries, veins, and nerves. An artery and vein penetrate each lobule group in company with the duct, and ramify between its lobules. The smallest arteries occasionally penetrate the lobules, but usually branches, diminishing in size, give off capillaries which enter the lobule and form a close net-work between the gland-acini.

"The capillaries of the island of Langerhans form a

glomerulus of tortuous, freely-anastomosing vessels, much thicker than those between the acini. A single afferent vessel like that of the glomerulus of the kidney does not enter this group of dilated capillaries, but numerous anastomoses make it continuous with the interacinar capillaries. When Berlin blue is injected through the aorta into the arteries of the pancreas, it not infrequently happens that in portions of the gland which are poorly injected the vessels of the island



CAMERA-LUCIDA TRACING OF THE LOBULE BOUNDARIES IN ONE OF A SERIES OF SECTIONS FROM THE SPLENIC END OF A CAT'S PANCREAS.

The majority of the lobules are well defined. Those marked *d*, *c*, *f*, *g*, and *h* are poorly outlined, but are found to be more readily distinguishable when traced through the series of secretions. The lobules, which are lettered (*a* to *o*), were traced through the series, and each was found to contain an island of Langerhans situated near its center. The section passes through the island in lobules *a*, *c*, *i*, *j*, and *n*. (*Eugene L. Opie.*)

are filled with the injected mass, while the surrounding capillaries are, for the most part, empty. If instead of soluble Berlin blue a granular injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the interacinar capillaries contain little of the injected material. The glomerular net-work is in very free communication with the smallest arteries, and apparently has a richer blood-supply than other parts of the lobule.

"In the human pancreas lobules and lobule groups are not so regularly arranged as in the cat. But both structures are more or less clearly definable. The lobules vary much in size, and are usually not clearly separated from one another. Though an island of Langerhans is often situated in the center of a more or less clearly defined lobule, no constancy of position is discoverable. The lobule groups are separated by relatively wide bands of loose areolar tissue in which are contained the medium-sized ducts, the blood-vessels, and the nerves. Within a lobule group the arteries and veins, which are side by side, do not, as in the cat, accompany the ducts."

The multiplicity of facts reviewed in the foregoing pages and the intricacy of the whole question make it necessary to collate and group in logical sequence the salient features of each subject discussed, in order to render a fruitful comparison of their merits possible. Not only are we required to analyze the questions involved in the light of the solid data that the last forty years have furnished,—*i.e.*, since Schiff first studied the relations between the spleen and the pancreas,—but all these must likewise be sustained by, and be in accord with, the functional mechanisms of the organs involved as I interpret them if my own views are well founded. If they are, they must necessarily assist us greatly in elucidating the various problems, physiological and pathological, to which reference has been made, since the very elements which they introduce bear upon a predominating factor in all these processes: *i.e.*, oxidation. To this subdivision of the subject we will, therefore, turn our attention.

Can we ascribe to oxygen, or rather to the oxidizing substance of the blood, the conversion of pancreatic trypsinogen into trypsin? We have seen that in both the spleen and pancreas the oxidizing substance seems, as elsewhere, to play the main functional rôle; the extrinsic and intrinsic vessels are disposed in a similar manner as regards their nervous relations, and vasodilation calculated to increase the flow of blood through both organs is similar. Moreover, we have seen that in the spleen the dilation incident upon malarial intoxication could be traced to the adrenals,—the primary source of excessive oxidation,—while in toxic glycosuria we obtained

as clear evidence that overactivity of the pancreas could also be ascribed to these organs. Again, the ease with which oxygen is thought to convert trypsinogen into trypsin—a mere current of oxygen through a solution of zymogen sufficing to produce trypsin—has been fully emphasized. Besides Heidenhain's labors in this connection, we need but recall Schiff's experiment with the two halves of a pancreas, one of which was infused at once and the other left exposed to the air a day, with the result that the latter alone proved active; and also that of Herzen, in which an infusion of active spleen mixed with an infusion of inactive (hence zymogen-laden) pancreas proved very active, while a pancreatic infusion mixed with one of inactive spleen digested nothing. Heidenhain ascribed to oxidation the conversion into trypsin, in this experiment. Indeed, when we consider the wealth of oxygen in the blood supplied the pancreas, direct from the lungs via the cœliac axis, it would seem as if it should be the predominating factor of the conversion processes involved.

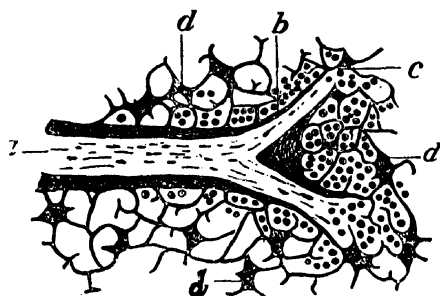
And yet, the oxidizing substance being a constituent of the blood-plasma, it would have to penetrate into the ducts *per se* and *as* oxidizing substance in order to carry out the required reaction. There is no evidence that a direct channel, such as there is in the spleen, by means of which the capillaries directly pour their blood into the secreting structures, exists. As may be seen in the annexed illustration, the splenic vessels actually terminate in the latter; "their walls become much attenuated, lose their tubular character, and the cells of the lymphoid tissue of which they are composed become altered, presenting a branched appearance and acquiring processes which are directly connected with the processes of the sustentacular cells of the pulp."³³

Nor is there evidence that canaliculi such as those of the hepatic cell exist by means of which the blood-plasma or its contents may directly find their way to a structure corresponding to bile-channels, which in the pancreas would be represented by the ducts. Langerhans long ago demonstrated that canaliculi were present in the lobules between the epithelia;

³³ Pickering Pick and Howden: "Gray's Anatomy," 1901.

cells, but these, besides being pyriform, terminate as blind pouches, with their orifice directed toward the glandular lumen. Saviotti also found these minute, delicate, pouch-like channels. Ramón y Cajal, using the Golgi method, found that they sent offshoots into the cells themselves, but that these also ended as blind pouches, their ampullar dilations never reaching beyond the line which separates the granular portion of the cell from the clear area. It is evident that these constitute collecting channels for the products of glandular metabolism; a further indication that no free channel between the blood-stream and the ducts exists.

Indeed, experimental proof to this effect is available: When the histological examinations of Kühne and Opie were



TERMINATION OF SMALL BLOOD-VESSELS IN THE SPLEEN. (Gray.)

a, Small artery. b, Vessel undergoing lymphoid change. c, Vessel continuous with supporting cells. d, Supporting cells.

mentioned on page 394, it was noted that material injected into the *duct* of the gland did not penetrate the islands of Langerhans. If, on the other hand, Opie's observation that injections of Berlin blue often filled the vessels of the island *per se*, leaving the majority of surrounding capillaries empty, is considered in this connection, it is evident that there can be no direct communication between ducts and blood-stream through either the islands of Langerhans or the glandular lobules that contain them. This involves an all-important deduction, however, viz.: that the splenic ferment, as well as the oxidizing substance, merely passes through the pancreas in transit, the latter, in its usual capacity of reagent, being intended only to activate function.

But how, under these circumstances, can we account for the experimental results reached by Schiff and Herzen, Heidenhain, Lépine, Pachon and Gachet, and Popelski? All these observers in one way or another have unquestionably shown a direct relationship between the blood-serum and trypsinogen, Heidenhain and Popelski considering oxygen as the converting agency, with solid experimental data to sustain them; Schiff, Herzen, and the other investigators mentioned attributing to the splenic ferment the same mission, with equally strong experimental backing. How account, for example, for the results observed in the following experiment of Herzen's? Two fasting dogs, having received all the meat they could eat, were at once submitted to ligation of the pylorus, bile-duct, and jejunal end of the duodenum, and also, in one of the dogs, of the hilum of the spleen. Albumin having been introduced into the duodenum, both dogs were killed after seven hours. In the dog with ligated splenic hilum the albumin was intact; in that in which the splenic vessels were free, the albumin had disappeared. This and other experiments to which we have referred may, indeed, be said to prove—whichever be the prevailing converting agency—that a communication between the blood-channels and the ducts exists.

We have seen that there is no evidence to show that the acini in direct communication with the ducts also open into the blood-vessels; these, as elsewhere, form a close-net-work around the acini, but they do not open into the blind pouches of the latter. Could the communicating channels traverse the islands of Langerhans? That these organs do not possess such channels or even ducts has been shown by Dogiel,³⁴ who studied this question in a well-preserved human pancreas treated by the chrome-silver method, and in which the gland-ducts, "even in their finest intra-alveolar branches, were well stained." Yet these structures possess morphological characteristics that are suggestive. Dogiel, for example, found that they possessed relatively large capillaries located in the cellular trabeculae. All investigators seem to agree upon the unusual size of those vessels. Kühne and Lea define the islands as "glomerular

³⁴ Dogiel: Böhm and von Davidoff, *Loc. cit.*

structures composed of *dilated* and tortuous capillaries." Opie calls them "vascular islets" which are in "very free communication with the smallest arteries and apparently have a richer blood-supply than other parts of the lobule." That these dilated arteries are possessed of special functions is suggested by the fact that, "if, instead of a solution of Berlin blue, a *granular* injection mass—for example, cinnabar or ultramarine blue—is used, the islands may be injected, while the intra-acinar capillaries contain little of the injected material." They appear to constitute alveoli or ampullæ rather than true vascular channels, in which what blood passes through them is submitted to some kind of process.

An interesting feature in this connection was noted by Opie, viz.: the fact that the cells of the islands of Langerhans are in some instances continuous with the regular glandular elements of the organ, in such a manner as to prolong the ducts of the latter by encircling them. "Occasionally," says the author, "one sees, apparently within the islands, cells arranged, as in the acini, about a central lumen, and, indeed, in many instances, it is difficult to convince one's self that they do not form part of it." This intimate relationship between the two sets of glandular elements is further emphasized by the manner in which their capillaries are related. While the smaller arteries or arterioles ramify between the lobules and supply the net-work of capillaries to the acini, they also communicate with the tortuous and dilated vessels of the islands of Langerhans; so that the latter, as regards their vascular relations, really constitute glomerular expansions and offshoots of the regular acini's blood-channels. We thus have two sets of superposed glands around a common duct, the upper, or common acini, pouring their own secretion (or granules) into it through their microscopical ducts; the lower, those of the islands—possessed of no ducts or other orifices—presenting their dilated capillaries or alveolar walls so as to cause them to face, and perhaps slightly project into its lumen. If we now replace by an active circulation through all these vessels the cinnabar or ultramarine-blue injections referred to above, the accumulation of the latter in the islands distinctly points to a similar process during life: *i.e.*, accumulation of blood and

its normal result (with narrower blood-vessels at each end of the glomerulus): *i.e.*, centrifugal pressure.

If we now conjoin Opie's remark—"the impression is produced that the columns of the island are in continuity with cells having an acinar arrangement"—and Mall's observation, in his study of the microscopical anatomy of the spleen,—that "the ampullæ and venous plexus have very porous walls which permit fluids to pass through with great ease . . ."—it seems probable that we hold the key to the situation. Indeed, what have we in the dilated glomerules of capillaries of the islands of Langerhans but vascular ampullæ? Centrifugal pressure under the circulatory conditions mentioned can have but one result: *i.e.*, *filtration of the blood-fluids through the ampullar walls and into the ducts.*

It is, perhaps, unnecessary to point to the fact that, besides being the only functional mechanism warranted by the anatomical structures present, it also meets all the requirements of the well-founded experimental data adduced. The precision with which it seems to harmonize the two seemingly antagonistic features of the general function represented—*i.e.*, the Schiff-Herzen spleno-pancreatic process and the Heidenhain zymogen-oxidation process—is also noticeable. If it is also realized that all these elements of the general function now fall sequentially in the normal order of their physiological usefulness, it will become apparent that I must have reached a solution—that submitted below—worthy of confidence:—

1. *The splenic ferment secreted into the splenic vein is carried to the portal vein and by this vessel through the liver, thence by the hepatic vein to the inferior vena cava, and after passing through the cardiopulmonary circuit is distributed throughout the entire organism.*

2. *The quantity of splenic ferment distributed to the pancreas is proportionate to the amount of blood carried thereto by the pancreatic subdivisions of the splenic artery, and represents but a fraction of that supplied to the general circulation.*

3. *The splenic ferment distributed to the pancreas follows the course of its blood-channels, and is distributed to the cellular elements of the organ dissolved in the blood-plasma.*

4. *On reaching the cellular elements, the plasma, through its*

oxidizing substance (adrenoxidase), insures functional metabolism of both glandular structures present,—the lobular acini and their immanent structures, the islands of Langerhans,—which metabolism, during the passive, or inactive, state of the organ, ends in the formation of the secretion granules.

5. *When at the end of the fourth hour of general digestion the pancreatic ferments are required in the intestinal canal, the vagus incites, sustains, and governs the functional activity of both the pancreas and the spleen, and thus insures their synchronous action as long as the pancreatic ferments are needed.*

6. *Intrinsic-nerve (vagal) dilation of the arterioles that supply both the pancreatic lobules and the islands of Langerhans with capillaries constitutes, as elsewhere, the mechanism through which glandular activity is sustained; but, the islands' vascular ampullæ possessing no muscular layer, they become the seat, owing to their large size, of sufficient blood-pressure to cause the blood-plasma and its contained splenic ferment and oxidizing substance (adrenoxidase) to filtrate through their walls.*

7. *Some lobules are entirely composed of true secreting cells; others contain, besides, islands of Langerhans. In the latter lobules the secretion, therefore, consists of two different bodies: the granules of the true secreting cells and the blood-plasma derived by filtration from the islands.*

8. *The true secreting cells and those of the island bring in continuity and surrounding a common lumen (Opic), both bodies—(1) the zymogen, or trypsinogen-forming, granules, and (2) the plasma containing the splenic ferment and the oxidizing substance (adrenoxidase) meet in this common lumen, which connects with the terminal ramifications of the pancreatic duct.*

This is about as far as we can proceed at present, since we can only surmise that, as soon as the products referred to meet in the glandular lumen, the splenic ferment at once converts the trypsinogen granules into liquid trypsin. Interesting in this connection, however, is the fact, observed by Laguesse, that "long before the pancreas begins its functions as a digestive gland granules accumulate in the internal zones of the cells; and when these come into contact with the blood a portion of them appears as though dissolved." As is well known, this is precisely what happens even in true acini that do not belong to

lobules supplied with islands. When secretory activity occurs, the granules of the inner zone of the cells simply disappear in the central lumen; but how and in virtue of what agency they are transformed into secretion at this point has not been determined. In the lobules supplied with islands of Langerhans the effused serum more than satisfies this feature, since it supplies two agencies thought to be capable of converting the granules into trypsin; but what of the lobules deprived of islands? How are *their* granules converted?

To answer these questions we must first ascertain which of the ferments credited to the pancreas can be shown to originate in the true acini. We have seen that, when the hilum of the spleen is ligated and no splenic ferment can find its way to the blood, the digestion of albumin ceases. It is, therefore, evident that, in accordance with Herzen's view, the splenic ferment is a *sine qua non* in the process through which trypsinogen is converted into trypsin. But why does the oxidizing substance not continue the conversion after ligation of the splenic hilum? There is but one answer to this, viz.: Herzen's zymogen and trypsinogen are not similar bodies; while zymogen is converted into some pancreatic ferment by oxygen, trypsinogen is not, and always requires the splenic ferment.

To illustrate this fact we submit, *in extenso*, two of Gachet and Pachon's experiments, performed to show that it was the spleen's ferment, and not its hæmoglobin, that converted pro-trypsin, which they term "proferment." Believing that zymogen, which, as shown by Heidenhain, is very greedy for oxygen, and "proferment" are the same bodies, their aim is to prove that, injected in arterial blood, pancreatic ferments cannot be converted into trypsin therein. But, interpreted from our standpoint,—since the blood contains oxidizing substance which zymogen would readily take up,—these experiments prove that zymogen and their proferment (trypsinogen) differ, as stated.

"As the proferment of the pancreas becomes very easily transformed into trypsin under the influence of oxygen," say Gachet and Pachon, "it seems possible that splenic extracts, intensely colored by the hæmoglobin, should owe their trypsinogenous power to the fixed oxygen of hæmoglobin which

they hold in solution. If such is the case, arterial blood, richer in oxygen, should render a pancreatic infusion containing the proferment more active than venous blood. A. Herzen has already studied this question and antagonized it by means of appropriate experiments. On our side, we have tried to ascertain the value of this opinion in the following manner:—

“Experiment II.—The pancreas of a fasting dog was allowed to macerate two hours in ten times its volume of a saturated solution of boric acid. By decantation, 200 cubic centimeters of the maceration liquid were taken and distributed among four flasks: A, B, C, and D.

“To A were added 20 cubic centimeters of defibrinated *arterial* blood (obtained from the fasting dog).

“To B were added 20 cubic centimeters of defibrinated *venous* blood (obtained from the fasting dog).

“To C were added 20 cubic centimeters of *congested* spleen (aqueous maceration).

“To D were added 20 cubic centimeters of distilled water.

“These flasks, in each of which was introduced 1 cubic centimeter of albumin, were then placed in the oven at 39° C.

“At the end of 4 hours beginning digestion was observed in flask C; villousities appeared on the surface of the cube of albumin, which continued to be attacked in an energetic manner.

“A and B, after remaining in the oven 24 hours, did not show very clear traces of digestion. Their cubes of albumin presented slightly less sharp projections, and their angles were more rounded. The cube in flask D was slightly attacked.

“Experiment III.—The pancreas of a fasting dog was divided into three parts and triturated: the first alone; the second with 20 cubic centimeters of femoral arterial blood; the third with 20 cubic centimeters of venous blood, taken, as was the former, from a fasting dog. These were placed in flasks A, B, and C, containing each 150 cubic centimeters of boric-acid solution. After remaining 2 hours in the oven the peptonizing power of the decantation liquids was tried. Their proteolytic action was very slow; the first signs of digestion had appeared: in A after 16 hours of oven; in B and C after 20 hours. Digestion was not further advanced in the flask

containing arterial blood than it was in that containing venous blood.

"It can be seen that in these two experiments arterial blood showed itself as inactive as venous blood. One cannot, therefore, ascribe the unquestionable action of the extract of congested spleen upon the pancreatic proferment to the oxygen of splenic tissue."

There is one feature in this connection, however, which requires elucidation: the influence that the use of *fasting* dogs might have had on the experiments. We have seen that under these conditions suprarenal activity becomes reduced; the blood may, therefore, contain but a minimum of oxidizing substance. Herzen performed an experiment which not only confirms our conclusion that zymogen and trypsinogen are not identical bodies, but also shows that fasting does not influence the results just given. As Herzen's experiment has already been reviewed at length, we will only reproduce its salient points. The pancreas of a fasting dog (hence rich in trypsinogen and other ferment-forming agencies) was infused in glycerin, and this in turn was mixed with eight samples of blood (bled directly in double its quantity of glycerin), four being taken from a fasting dog and four from a dog in full digestion with its spleen greatly dilated. The four samples were taken in both animals from the femoral artery, the femoral vein, the splenic artery, and the splenic vein. Fibrin was then added to each sample. "After 1 hour there was still no trace of digestion under the influence of the femoral blood, arterial or venous, nor of the splenic arterial blood of the fasting dog; first traces of digestion were beginning to manifest themselves under the influence of the splenic *venous* blood of this animal. Digestion was rather advanced in the case of the femoral arterial and venous blood and splenic arterial blood of the *digesting* dog; the fibrin had almost entirely disappeared under the influence of the *splenic venous* blood of the same animal." This seems to us to confirm not only the view held by Herzen, that the splenic ferment is the only agency capable of converting trypsinogen into trypsin, but also that trypsinogen does not, like zymogen, possess affinity for oxygen.

This may be further demonstrated by showing that oxygen does exist in the blood, and that if we were dealing with zymogen it would be oxidized therein. The oxidation of sugar converted from glycogen, we have seen, represents the main factor in the production of functional energy in the muscles and other structures. That sugar occurs in the blood normally, but in small quantities, its combustion therein depending mainly—as in toxic glycosurias—upon suprarenal activity, we have also seen. The more these organs produce of their secretion, the greater is the proportion of oxidizing substance in the blood, and suprarenal insufficiency means a corresponding increase of sugar in the blood through imperfect oxidation. Hence the oxidizing substance is a sugar-destroying agency.

That an agent capable of consuming sugar exists in the blood was ascertained by Lépine in 1889, who named it “glycolytic enzyme.” Howell, referring to this substance, says: “It has been asserted by Lépine and Barral that there is normally present in the blood an enzyme capable of destroying sugar. Their theory rests upon the *undoubted fact that sugar added to blood outside the body soon disappears.*” This obviously constitutes another proof of the existence of oxidizing substance in the blood.

Howell, referring also to the supposed source of Lépine’s glycolytic enzyme, says, referring to the pathogenesis of glycosuria: “The most plausible theory suggested is that the internal secretion produced contains a special enzyme, glycolytic enzyme, whose presence in the blood is necessary for the consumption of sugar. Such an enzyme *may be obtained from the blood*, but it is not proved whether it is a normal constituent or whether it is produced after the blood is shed by the disintegration of some of its corpuscular elements.” . . . “It is interesting and suggestive to state, in this connection, that post-mortem examination in cases of diabetes mellitus in the human being has shown that this disease is associated in some instances with obvious alterations in the structure of the pancreas.” That the glycolytic enzyme is, as oxidizing substance, a normal constituent of the blood is obvious; but the interesting feature to determine now is whether, as believed by Lépine, the pancreas is the source of the ferment, since, if it

were, it would constitute an additional factor in this organ's physiological functions.

To which of the two pancreatic active structures can we hypothetically ascribe the formation of the glycolytic enzyme? Laguesse³⁵ has ascribed this function to the islands of Langerhans. That these structures underlie some physiological process in addition to that already analyzed by us is undoubted. The fact that they contain large nuclei shows that they are physiologically active. "The cells composing the islands resemble those of the acini," says Opie; "they have a large, round, occasionally oval, vesicular nucleus and a conspicuous cell-body." They must produce some ferment or its zymogen, for Ssobolew found that feeding animals on carbohydrates caused them—*i.e.*, their protoplasm—to become granular. This is indirectly confirmed by the fact that these bodies are often found diseased in diabetes. They had entirely disappeared in two of Ssobolew's cases. In a case of Opie³⁶ hyaline metamorphosis was strictly limited to the islands of Langerhans the glandular acini remaining intact. Flexner³⁷ refers to this cause of diabetes as follows: "That it depends upon an internal secretion supplied by the pancreas to the blood is highly probable. Whether this hypothetical secretion is the product of the cells of the islands of Langerhans is unproven."

The data bearing upon this source of diabetes are very few,—an unfortunate fact, since these particular structures seem to us to play the predominating rôle in the production of glycosurias of pancreatic origin, now that we have ascertained that they are, through their ampullæ, the only thoroughfares for the splenic ferment. Still, can we, with Laguesse, now consider them as the source of a glycolytic ferment? Were we to admit this possibility, we would find ourselves obliged to concede that the pancreas supplies the intestinal tract with a glycolytic ferment besides an amylolytic ferment, and we would have, as a result, the formation of maltose from food-starches and its immediate destruction by the glycolytic fer-

³⁵ Laguesse: *Loc. cit.*

³⁶ Opie: *Journal of Experimental Medicine*, March 25, 1901.

³⁷ Flexner: *University of Pennsylvania Medical Bulletin*, Jan., 1902.

ment, thus annulling the very important functions of sugar in the economy.

It is plain that the islands of Langerhans are not the source of a glycolytic ferment. Of course, Professor Lépine has never, that we know of, sustained this view, his contention being simply that the normal pancreas contains a glycolytic ferment which finds its way into the lymph and blood, in which it controls the consumption of sugar by the tissues. And his experimental evidence, in the light of our views, shows this to be the case, since it all goes to prove that the oxidizing substance which enters the pancreatic circulation is a glycolytic body. This does not mean that it acts therein as such; indeed, the organic cells at once take up its oxygen for their own functional interchanges, the blood returning to the splenic veins as venous blood. But it is nevertheless obvious that Lépine should have experimentally found, as he says, a glycolytic ferment in the pancreatic blood. All we show, therefore, is that Lépine's glycolytic ferment is probably the oxidizing substance.

But why should disease of the pancreas under these circumstances increase the proportion of sugar in the urine: a feature which Lépine ascribed to decrease of sugar destruction and to the fact that "these lesions decrease the source of the glycolytic ferment in the economy"? From our standpoint, of course, the adrenals are the original source of the oxidizing substance: *i.e.*, adrenal secretion *plus* oxygen. But does this account in an equally satisfactory manner for glycosuria? This introduces a very important feature of the entire analysis, one, indeed, bearing upon the pathogenesis of all forms of pancreatic diabetes.

We have previously referred to the fact that disease of the islands of Langerhans had been found to be a prominent causative factor of diabetes by various pathologists, and that Opie had witnessed a case in which these islands *alone* were diseased. This obviously points to the fact that, *if in accordance with our view the ampullæ of the islands are the pathways of the Schiff-Herzen splenic substance to the ducts*, we are dealing either with obstruction or impaired conversion of trypsinogen into trypsin, or both simultaneously. If, bearing this feature in mind, we review the list of pancreatic diseases that cause

glycosuria, it will become apparent that these two factors account for the phenomena observed in many cases: calculi, lipomatosis, hypertrophy, tumors, induration, and periglandular sclerosis. Atrophy,—a condition which in itself implies functional impairment,—on the other hand, constitutes the majority of the remaining pathological processes encountered post-mortem in this organ.

But the question which now imposes itself is this: Why and how does a condition that interferes with the conversion of trypsinogen into trypsin or that impedes the passage of the latter to the intestinal foodstuffs cause diabetes? The answer now seems plain, viz.: *because insufficiency of trypsin is followed by imperfect reduction of proteids to simpler bodies, resulting in the formation, or inadequate splitting, of toxic albuminoids.* In other words, impaired pancreatic action of the kind mentioned gives rise to toxic glycosuria.

Our interpretation of the general subject seems again to conciliate antagonistic views. Indeed, while Lépine³⁸ has affirmed that “the pancreas exercised a glycolytic influence,” Chauveau and Kaufmann have held the opposite: *i.e.*, that “glycolysis is not diminished in diabetes, and that diabetes is exclusively due to an increase in the production of glucose.” We have shown that the arterial blood of the pancreas does contain a glycolytic body,—the oxidizing substance,—but we have also—by our analysis of Cartier’s paper and other data—demonstrated that suprarenal overactivity was the underlying cause of toxic glycosuria: *i.e.*, a source of increased production of sugar. To further sustain this fact, we may recall that the coal-tar products, as already stated, possess a marked tendency to inhibit the functions of the adrenals, sufficiently, in some instances, to produce blood-disintegration. Lépine has himself observed that methæmoglobinuria could follow the use of anti-pyrin. This remedy is now classed among the most active agents at our disposal for the reduction of glycosuria. A remark of Professor Lépine proves this to be the case in another way. Referring to experiments conducted with the collaboration of Porteret, he says, regarding the action of

³⁸ Lépine: “Le Diabète,” Paris, 1899.

antipyrin, that, "in the cases in which it exercises an anti-diabetic action, this substance acts, not by activating the destruction of sugar, but *by preventing its formation.*"³⁹ This is due, as explained in the second volume, to the fact that antipyrin excites a center (the sympathetic center, also described in the second volume) whose purpose is to cause constriction of the arterioles after, as we have seen, they have been dilated by a cranial nerve. Antipyrin thus produces general constriction of the arterioles, and the blood admitted into the adrenals, pancreas, and liver—the main organs involved in diabetes—being reduced, the "formation" of sugar is actually prevented.

In view of these facts, what is the nature of the product the existence of which the prominent nuclei and the granules observed in the protoplasm of the islands indicate? This is elucidated by two other features just brought out, namely: (4) that glycosuria may be the result of intoxication by toxic albuminoid bodies incident upon an insufficiency of trypsin, and (5) that disease limited to the islands, as shown by Opie, can cause glycosuria. It is plain that, in the latter case, the permeability of the ampullæ being alone compromised, the pancreatic lobules that contain no islands are free as to the elimination of their secretion into the ducts. If they produce trypsinogen,—*i.e.*, trypsin,—why are the functions of the latter inhibited or absent as indicated by the glycosuria? The only logical answer to this question is that *the islands of Langerhans alone secrete trypsinogen.*

This fact, when added to others reviewed, normally leads to another deduction: *i.e.*, that, in addition to any other function it may possess, *the spleen and the islands of Langerhans are functionally united in the formation of a ferment,—trypsin,—which is able to digest albuminoid bodies in the blood-stream.*

We can now readily understand why the spleen and the pancreas are so intimately connected through their nervous supply. Indeed, this throws light upon a phenomenon which we approach almost with diffidence: *i.e.*, Claude Bernard's experimental glycosuria obtained by puncturing the medulla oblongata. "That pathological conditions of the central nerv-

³⁹ The italics are Professor Lépine's.

ous system and perhaps of the sympathetic and larger peripheral nerves may give rise to glycosuria and diabetes is, of course, established," says Flexner.⁴⁰ "The number of neuropathic conditions in which one or the other of these has been found is now considerable. The one definite condition, *the effect of which is constant*, is Claude Bernard's *piqûre*, and, as bearing out the physiological relationship existing between *certain unknown structures* in the floor of the fourth ventricle and the glycogen-store in the liver, may be cited the instances of lesions (hæmorrhages, softening, tumors) in man observed in this situation with which glycosuria has been associated. That cerebral and perhaps spinal disturbances other than those in the region of the fourth ventricle may be associated with or followed by diabetes many clinical cases prove. On the other hand, there is no evidence that would show that it is the direct influence of the central nervous system upon the carbohydrate metabolism that produces hyperglycæmia and glycosuria. Indeed, the experiments in which *the splanchnics were sectioned after piquê* (Claude Bernard and others) *without producing glycosuria* show the necessity of the interaction of other organs."⁴¹

Read in the light of all we have said,—particularly the allusion to the relationship between the medulla and the suprarenal glands through the splanchnic,—these lines, from so competent an observer as Flexner, and which confirm those of Cartier as to the action of section of the splanchnic, seem to us to afford confirmatory evidence based upon the most solid labors of the last half-century and to embody Claude Bernard's own sanction. To analyze their far-reaching meaning would involve the repetition of what has been said in all this volume. Formulated as a deduction, the functional relationship between the floor of the fourth ventricle and glycosuria would be as follows: *Puncture of the floor of the fourth ventricle (Claude Bernard) causes glycosuria because the increased blood-supply in the injured area incident upon the local reparative process correspondingly excites the normal structures around this area. As*

⁴⁰ Flexner: *Loc. cit.*

⁴¹ All italics are our own.

these structures include nerve-fibers which govern the adrenals, these organs are stimulated and glycosuria is produced by their secretion.

What we might term the intrinsic functions of the pancreas have now been analyzed; the importance—also in conjunction with the spleen—of its *extrinsic* functions must now be inquired into. Foster states that “a pancreas taken fresh from the body, even during full digestion, *contains but little ready-made ferment*, though there is present in it a body which, by some kind of decomposition, *gives birth to the ferment.*”⁴² . . . To this body, this mother of the ferment, which has not at present been satisfactorily isolated, but which appears to be a complex body, splitting up into the ferment, which, as we have seen, is, at all events, not certainly a proteid body, and into an undeniably proteid body, the name of *zymogen* has been applied. But it is better to reserve the term *zymogen* as a generic name for all such bodies as, not being themselves actual ferments, may by internal changes give rise to ferments,—for all ‘mothers of ferment,’ in fact,—and to give to the particular mother of the pancreatic proteolytic ferment the name *trypsinogen*.” In other words, and in accord with prevailing custom, each *zymogen* is named from the ferment it produces: the *zymogen* of trypsin being “trypsinogen”; that of pepsin, “pepsinogen,” etc. It is therefore permissible to use the term “*amyllopsinogen*” as the main product of the true lobular acini to differentiate it from *trypsinogen*, the product of the islands of Langerhans, reserving the term *zymogen* as a generic term for all pancreatic ferments. As “*zymogen*” under these conditions, it preserves characteristics attributed to it by Heidenhain; it is soluble in water, in which it is split, after exposure to the air, into trypsin, etc. (Charles). The conversion of *trypsinogen* into trypsin has been ascribed to oxygen; but if my views are sound and the former is the normal product of the islands, the portion distributed through the pancreatic ducts is intimately combined with the splenic ferment in the ampullæ as fast as formed, so that it can never be obtained as *trypsinogen*. Hence, oxygen will split *zymogen* into trypsin, etc.; but trypsin is not oxidized *trypsinogen*.

⁴² The italics are the author's.

We have followed the course of the blood from the splenic vein and back again to the splenic artery which supplies branches to the pancreas, and we have seen that on its way through the latter the arterial blood surrenders its oxygen to the cells and its splenic substance to the islands. The dominant feature of the extrinsic functions of the pancreas is its power to destroy albuminoid toxic bodies, and it is evident that the splenic ferment, the mission of which is merely to unite with trypsinogen to form trypsin, cannot do this alone. It is *trypsin* that constitutes the antitoxic body, and it is the pancreas, therefore, that supplies it to the organism. How does it penetrate the general blood-stream?

Now that we have ascertained that the islands of Langerhans are the seat of manufacture, as it were, of at least a part of this antitoxic agency, and that it collects (combined) in the ampullæ, the manner in which the general circulation becomes supplied with it is clear: *i.e.*, the quantity that permeates through the ampullar walls is but a portion of their contents, and the rest is swept away with the blood and reaches the splenic vein through the pancreatic veins. But this does not mean that trypsinogen may not be carried alone in the same manner to the splenic vein and therein combine with the splenic ferment to form trypsin. In fact, this must constitute the prevailing process, if the anatomical distribution of the islands of Langerhans, as observed by Opie, can serve as guide.

As we have seen, Opie found that the islands of Langerhans were over three times as numerous in the splenic end of the pancreas as elsewhere, and that the part of the organ not in communication with the splenic vein—*i.e.*, the extremity of the descending arm—contained none. Moreover, each lobule in the splenic end of the organ was found to contain an island: a very suggestive fact. The tip of the pancreas, which is almost in contact with the spleen, thus marks the starting-point of the islands; so that trypsinogen begins to enter the splenic vein almost at the hilum. Pancreas and splenic vein being connected by several short venous radicles at about regular intervals, the blood in the vein must become literally saturated with trypsinogen, and its blood be replete with trypsin when it reaches the portal vein, during the active stage of

intestino-portal digestion. We have seen in Herzen's experiment how rapidly albumin was digested with blood obtained from the splenic vein during this stage.

That the amylolytic ferment derived from Heidenhain's zymogen is also carried to the splenic vein is probable. I have shown that it was through the effects of this ferment that the liver glycogen was converted into sugar, and that the importance of the latter, when distributed to the muscles and other structures in which it is consumed, was very great. That the conversion of glycogen into sugar is a continuous process and that it is independent of digestion are recognized facts,—and necessarily so, since the activity of the functions that entail the use of glycogen may at any moment be increased, the tissues requiring replenishment to a correspondingly great degree at the expense of the liver reserve. How could this predominating function be carried on in the perfect manner that it is, were it connected with, or did it depend upon, any digestive process? Again, if present views prevailed and the amylolytic ferment were to only reach the liver after being secreted in the duodenum by the pancreas, then absorbed by the venules of the villi, how could we account for the conversion of glycogen between the periods of active digestion? That the intestinal tract is not the channel traversed by the portion of pancreatic amyllopsin devolved to the conversion of glycogen into sugar is also suggested by familiar experiments.

We have seen that the insertion of a piece of pancreas into the tissues of an animal showing marked glycosuria, after removal of the pancreas, will cause it to disappear. This apparently constitutes a direct contradiction of all the foregoing statements; but such is not the case in reality. Minkowski⁴³ confirmed the fact, observed by other investigators, that glycogen quickly disappears after removal of the pancreas. This indicates two important features: *i.e.*, that glycogen is no longer formed after removal of the pancreas, and that some other agency converts it into sugar. Why removal of the pancreas should prevent the formation of glycogen may probably be accounted for by the fact that the absence of trypsin causes

⁴³ Minkowski: *Berliner klin. Wochenschrift*, No. 5, 1892.

the digestion of albumins in the duodenum to cease, as shown in the Schiff-Herzen experiments. That the conversion of food-starches into maltose is also, owing to the absence of amyllopsin, arrested, is evident. The only substitute for this ferment available is ptyalin; but though the salivary secretion—at least, its ptyalin—is quantitatively increased after removal of the pancreas, it is inadequate to convert all the starch required to compensate for the glycogen used. The glycogen, gradually converted by what ptyalin is swallowed with the saliva between meals, therefore disappears. The fact that ptyalin converts starch partly into dextrose greatly hastens the disappearance of the glycogen, the primary sugar of which is mainly maltose. It would seem, therefore, *that the glycosuria following extirpation of the pancreas is due to the action of ptyalin upon food-starches.*

That the salivary secretion is gradually increased after removal of the pancreas is sustained by experimental evidence. Aldehoff⁴⁴ observed that glycosuria only appeared from 24 to 48 hours after the operation in turtles; in frogs it only appeared after four or five days, "slight at first, becoming more intense later on." Minkowski⁴⁵ found that it sets in after two or three days in dogs, under the same conditions. Again, during its passage through the stomach ptyalin acquires increased energy as a ferment. Charles⁴⁶ refers to this question as follows: "Chittenden and Griswold find that the presence of acid, as hydrochloric acid, to the amount of 0.005 per cent. decidedly increases the diastatic action, while an increase beyond this diminishes it, the action stopping with solutions of acid from 0.1 to 0.4 per cent.; the diastatic action of the saliva would, therefore, appear soon to cease in the stomach, but *the peptones* in that organ exercise a decided influence on salivary digestion, stimulating the ferment to *increased action*, particularly in presence of acid, which by itself may completely prevent the conversion of starch into sugar." Mering found that starch acted on by saliva yielded dextrin and maltose at first, then after some time grape-sugar.

⁴⁴ Aldehoff: *Zeitschrift für Biologie*, Munich, Bd. xxviii, p. 293, 1892.

⁴⁵ Minkowski: *Loc. cit.*

⁴⁶ Charles: *Loc. cit.*

Yet, glycosuria so produced may, we have seen, be prevented by grafting a fragment of pancreas under the skin. Minkowski⁴⁷ grafted such fragments in the dog, cat, and pig, removed from the pancreas of these animals. When the graft had become adherent and functionally active, he removed the rest of the pancreas. No glycosuria appeared until the grafted portion itself had been removed. Besides indicating that ptyalin glycosuria prevails after resection of the pancreas, the fact that grafts can preserve normal functions clearly shows that the intestinal canal is not the only region wherein splitting of carbohydrates and proteids may occur. Each graft evidently received its blood through newly-formed vessels. This blood doubtless contained splenic ferment, since, as previously stated, the greater portion of this ferment really enters the general circulation *via* the liver, and ultimately reaches the portal circulation, probably by the hepatic artery, in the experimental animals. Such being the case, it is evident that *the splenic vein can, besides the intestinal villi, serve as a channel for the transmission of the pancreatic and splenic ferments to the liver.*

Here, again, however, we are brought to realize that the splenic ferment is not merely a local agency, but one which during spleno-pancreatic activity forms part of the entire blood-stream. I have given striking evidence of this in Herzen's experiment with blood taken from various arteries and veins. We saw that blood taken from the femoral vessels (arterial and venous) of a dog in full splenic digestion proved active in digesting albumin, and that the blood of the splenic vein was exceedingly active. Indeed, the blood which is so active in the pancreas originates from the cœliac axis, lungs, heart, etc.,—*i.e.*, from the general circulation,—and only contains the proportion of splenic ferment which the entire blood-stream contains. But a question suggests itself here: If, by the combination of trypsinogen and the splenic ferment, trypsin is formed, is it not trypsin-laden blood that re-enters the pancreas? Trypsin *would* re-enter this organ were the relative proportions of the two bodies not regulated by the vagus. As

⁴⁷ Minkowski: *Loc. cit.*

we find that a slight excess of splenic ferment will serve the physiological process in the pancreas,—to supply the intestinal canal,—if we grant the vagus even one-tenth of the truly wonderful prerogatives it seems to possess, we can readily assume that, by regulating the quantities of either ferment allowed to enter the blood-stream, it provides just the excess of splenic ferment in the pancreas to insure perfect function during the digestive process: all features which indicate that *trypsin is a constituent of the entire blood-stream when albuminoids are undergoing digestion in the alimentary channels.*

The far-reaching meaning of all this is suggested in the following deductions:—

1. *The cleavage processes to which trypsin submits albumins in the intestinal canal include the preliminary steps of a protective function.*

2. *The spleno-pancreatic internal secretion is represented by the trypsin which reaches the portal vein by way of the splenic vein, and which continues in the blood-stream the cleavage processes begun in the intestinal canal.*

3. *The main function of the spleno-pancreatic secretion, trypsin, in the blood-stream is to protect the organism from the effects of the toxic derivatives of albuminoid bodies of endogenous or exogenous origin, including toxins.*

CHAPTER IX.

THE ADRENAL SYSTEM IN THE FUNCTIONS OF THE HEART AND LUNGS.

I HAVE repeatedly referred to the functional connection between the secretion of the adrenals and the heart. Is this connection direct or is it indirect? In other words, is it the result of a direct stimulation of the heart-muscle such as is produced by suprarenal extract, or of the stimulating effect to which the increase of oxidizing processes, including those of the cardiac cerebro-spinal centers, give rise? Analysis of this question tends to show that both processes prevail simultaneously when from any cause the adrenals become over-active.

THE ADRENAL SECRETION AS THE SOURCE OF THE FUNC- TIONAL ACTIVITY OF THE RIGHT HEART.

As freshly-oxidized blood is constantly being supplied to *both* sides of the heart, the specific action of digitalis upon the right heart to which I have referred cannot be ascribed to the oxidizing substance. Again, it would seem that the suprarenal secretion itself could hardly be credited with a local stimulating action upon the cardiac walls when the thickness of the myocardium is recalled, unless the latter be provided with channels calculated to insure the penetration of the secretion to its deeper tissues. Not only do such channels exist, however, but they are so disposed as to enable the adrenal active principle to permeate the entire myocardium and be equally distributed among the contractile elements. The channels to which I ascribe such important functions have been known as the "foramina of Thebesius."

These canals are described in Gray's "Anatomy" as follows: "The foramina Thebesii are numerous minute apertures, the mouths of small veins (*venæ cordis minimæ*), which *open* on various parts of the inner surface of the auricle. They *return* the blood directly from the muscular substance of the

heart. Some of these foramina are minute depressions in the walls of the heart, presenting a closed extremity."¹ This information would afford but little light could we not supplement it with an excellent paper by F. H. Pratt,² in which the *nutrition* of the heart through the vessels of Thebesius and the coronary veins is studied. How much we are indebted to the author for his investigations is suggested by the following remarks: "So far as I have been able to determine, no *experimental* physiological work has ever before been done on the vessels of Thebesius; all opinion regarding their functional importance has rested upon the assumption that they only serve as veins, conveying a part of the venous blood from the coronary capillaries through the foramina Thebesii into the cavities of the heart."

After referring to the labors of Thebesius (1708), Vieussens (1757), Haller (1786), and Abernethy (1798), the author reviews the more modern investigations of Bochdalek,³ which led to the conclusion "that the greater number of the small openings on the inner surface of the right as well as the left auricle, which from early times have borne the name of foramina Thebesii, represent the mouths of little veins that, *often uniting into larger vessels*, course with many branches *through the auricular walls*." Langer's researches⁴ on the foramina of the human heart are next analyzed. "With the aid of the blow-pipe, and by means of a watery injection-mass colored with Berlin blue, he demonstrated these foramina *in all the cavities* of the heart. He succeeded in injecting the vessels of Thebesius not only from the coronary vessels, but from the *endocardial* surfaces as well. Bochdalek's observations regarding the presence in both auricles of foramina Thebesii were thus confirmed, and the fact of a communication between the coronary vessels and each of the four cavities of the heart was thoroughly established. The foramina which Langer found on the endocardial surfaces of both ventricles were similar to those in the auricles, but much smaller. They

¹ All italics are our own.

² F. H. Pratt: *American Journal of Physiology*, vol. 1, p. 86, 1898.

³ Bochdalek: *Archiv für Anat. u. Phys. u. wiss. Med.*, Leipzig, p. 314, 1868.

⁴ Langer: *Sitzb. der k. Akad. der Wissensch. zu Wien*, 1880, Bd. lxxxii, 3 Abth., p. 25.

were most conspicuous on the papillary muscles and in the *neighborhood of the great vessels*, being less easily seen in the region of the apex, where they were obscured by the trabecular net-work."

Very suggestive in connection with my own views are also the observations of Gad⁵ on the vessels of Thebesius in the ox, and to which Pratt refers in the following words: "In the method which he describes for demonstrating the action of the valves of the *left heart*, wherein water under pressure is made to fill the ventricle and aorta, he noticed that water flowed into the *right heart* from the foramina Thebesii. On illuminating the interior of the left ventricle he was enabled to see fine, blood-stained streams issuing from the endocardial wall into the clear water with which the cavity was filled." Finally he reviews the labors of Magrath and Kennedy,⁶ who, "working with artificial circulations of defibrinated blood on the isolated heart of the cat, observed that a small portion of the *coronary blood* found its way into the *left ventricle*. The only possible source of access other than from the vessels of Thebesius was leakage past the aortic valves. This leakage, as shown by a manometer-record of aortic pressure, did not occur." The author closes his review of the literature of the subject with the statement that "notwithstanding these painstaking observations, the vessels of Thebesius still occupy a very obscure position in anatomical literature. Foramina Thebesii are referred to as constant in the right auricle, forming in part the mouths of small veins. Their occurrence in the left auricle is occasionally mentioned. But the fact that *the vessels of Thebesius open into all the chambers of the heart*—ventricles as well as auricles—is hardly recognized."⁷

In the author's own experiments, various agents were injected at a constant pressure, through the coronaries of fresh, often still living, hearts of the rabbit and dog. They showed that liquids in these vessels penetrate into the heart cavities through the endocardial foramina, thus verifying the foregoing

⁵ Gad: *Archiv für Physiologie*, p. 380, 1886.

⁶ Magrath and Kennedy: *Journal of Experimental Medicine*, vol. ii, p. 13, 1897.

⁷ All italics are our own.

data. As the cannula was tied directly into the artery, the liquid could only reach the cavities through the foramina, while in all experiments care was taken to avoid high pressures. In the heart of the ox the endocardial depressions were found "regularly *larger in the auricles than in the ventricles,*" while in the right auricle "they may," he states, "be provided with thin, single valves, *especially about the origin of the great veins.*" In the left auricle the depressions are fewer in number and unprovided with valves. "Foramina Thebesii are *never absent from the ventricles,*" says Dr. Pratt. "In the *right ventricle,* which is *especially well provided with them,* the larger number are seen upon the septal wall. It is often *much more difficult to find them in the left ventricle,* although a diligent search is never without a reward" . . . "structures, accessory to these ventricular foramina, which might in any way serve the office of valves I have not seen." . . . "On the injection of the vessels of Thebesius with air by means of the blow-pipe applied to the foramina, characteristic, fine, *subendocardial ramifications,* which very frequently conduct the air into other Thebesian systems, or *even into the great coronary veins* will seldom fail to appear." The latter point is also sustained by experimental evidence.

The fact that the right side of the heart is endowed with a more perfect system of canalization than the left is suggested by the following remarks: "The ease with which injections of air and blood could be made to demonstrate the connection between the vessels of Thebesius and the coronary veins caused me to doubt the opinion expressed by Langer that the foramina Thebesii in the ventricles *communicate with the veins by capillaries alone.* To settle this point, I injected the coronary veins of the ox with starch and celloidin masses, both too thick to pass the capillaries, and found that even these emerged from the foramina Thebesii of the right ventricle. So intimate a connection, however, between the coronary veins and the vessels entering the *left ventricle I have not yet been able to demonstrate.*" The author also says: "By means of a very successful corrosion preparation, made by injecting the veins of an ox-heart with celloidin, I was able to trace the communication. In this preparation the position of some of the foramina

Thebesii was marked by small disks of the hardened mass formed by the oozing out of the celloidin upon the endocardium. These foramina were shown to be connected with the smaller *coronary veins* by fine branches. The still finer ramifications which, as Langer has demonstrated, lead from the foramina and branch directly into capillaries were here uninjected; they would appear only when injected from the foramina themselves."

The only connection between the vessels of Thebesius and the coronary arteries that he could find, notwithstanding repeated attempts, was by capillaries. Boehdalek having observed that the foramina of one auricle communicated with those of the other, he was able by blow-pipe injection to verify the correctness of this view, the air of one auricle having passed out through a similar exit into the other.

To sustain his view that the nutrition of the heart may be carried through the vessels of Thebesius some time after the coronary arteries are absolutely obliterated, a number of experiments are related. Thus, fluid introduced into the ventricle of an isolated heart, by means of a cannula passed down to this cavity, and tightly held *in situ* by a ligature passed around the auriculo-ventricular groove, only found its way through the vessels of Thebesius. Defibrinated blood, inserted into the organ through this cannula, brought on, often within one minute, "strongly marked, co-ordinated contraction of the ventricle." As the blood thus introduced would become venous, the action would become gradually reduced, but renewal of the blood would at once cause the heart to resume its normal action. "With a periodic supply of blood," says the author, "and with favorable temperature and moisture this may continue several hours." That mere mechanical stimulation by distension did not cause the phenomena witnessed is demonstrated by the alternate use of Ringer's solution and defibrinated blood. While the solution failed to sustain contractions, blood always succeeded.

Another experiment served to demonstrate that a true circulation could take place between the vessels of Thebesius and the coronary veins. The organ being disposed as stated above, two of the coronary *veins* were incised; "a small, but

steady, stream of venous blood issued from them." Under the same conditions the descending branch of the left coronary artery was opened. "No flow of blood occurred from the artery, although there was a free escape from an incision in an accompanying vein." In still another experiment the trunks of both coronary arteries were ligated and the ligature around the ventricles omitted. "The supply-cannula was tied into the ventricle through the oarta. On the introduction of blood the left ventricle alone began to beat strongly and regularly . . . the blood found its way in part into the right ventricle, coming of necessity through the walls. . . ." The blood from the left ventricle had thus found its way into the right one. Finally, he refers to the striking analogy which this nutritional system presents to that of the frog and cat. In the frog the heart is almost entirely nourished "through the branching passages that carry the blood from the interior of the heart nearly to the pericardial surface."

On the strength of all this evidence, Dr. Pratt concludes (giving only the features that bear directly upon the question we are analyzing) that: "1. The vessels of Thebesius open from the ventricles and auricles into a system of fine branches that communicate with the coronary arteries and veins by means of capillaries, and with the veins—but not with the arteries—by passages of somewhat larger size. 2. These vessels are capable of bringing from the ventricular cavities to the heart-muscle sufficient nutriment to maintain long-continued, rhythmic contractions. 3. The heart may also be effectively nourished by means of a flow of blood from the auricle back into the coronary sinus and veins." The author concludes with the very appropriate remark: "It is evident that the nutrition through the vessels of Thebesius and the coronary veins must modify in no slight degree the existing views of the nutrition of the mammalian heart, and of the manner in which infarction of the heart takes place." The clinical features of this question will be considered elsewhere.

Viewed from my standpoint, *the vessels of Thebesius are more concerned with the dynamics of the heart than with the nutrition of this organ*, though the latter function is not to be ignored, particularly in the sense emphasized by Pratt: *i.e.*,

as a source of compensation. That nutrition of the left heart, auricle and ventricle, constantly filled with arterial blood, can result from a flow of the latter through the Thebesian vessels seems clear, but nutrition can hardly be associated with a similar process in the *right* heart, with nothing but *venous* blood to propel through the Thebesian channels. That nutrition, the recognized prerogative of arterial blood, owing to its oxygen, cannot be the active factor here is evident.

The right heart seems, judging from the anatomical arrangement of the parts concerned in the process, to play a physiological function of a special kind. While the Thebesian openings are larger in the auricles than in the ventricles, in the left auricle they are also fewer than in the right; but even more suggestive is the fact that, while some openings in the right auricle are supplied with valves, none have been found in those of the left. Again, both ventricles are supplied with foramina: the right ventricle is particularly well provided with them, while they are difficult to find in the left one. That the septal wall should show them most clearly on the right side is also suggestive. Evidently a similar condition exists between the auricles, as suggested by Bochdalek and confirmed by Pratt; but the fact that limited information supplied by works on anatomy usually covers only those of the right auricle points to greater prominence of the latter. Thus, Gray⁸ states that the *venæ Thebesii* open "on the inner surface of the right auricle." Finally, the openings supplied with valves are in the right auricle, as we have seen; but they are also stated to be most conspicuous in the neighborhood of the great vessels; hence it must only be the Thebesian openings around the great vessels of the right auricle—the *venæ cavæ* and the pulmonary artery—that are provided with valves.

If we can now ascertain whether the current which enters the Thebesian vessels from the right auricle is shut *out* in this location, or secured *within* the channels, according to the manner in which the valves close,—*i.e.*, inwardly or outwardly,—we will be able to decide whether *venous* blood from the *venæ*

⁸ Gray: "Anatomy," edition, 1901, p. 622.

cavæ or arterial blood from the lungs circulates in the Thebesian system.

Bochdalek found that many of these openings in the auricles "presented the appearance of blind depressions, since they were often covered with single valves in such a way as to resist investigation with the blow-pipe" . . . "some were slit-like, resembling the mouths of the ureters; still others were large, round depressions, with smaller openings at the bottom." The first remark suggests that the openings serve as exits into the auricle, while the second points to the contrary, since it is difficult to conceive of a *depression* with "openings at the bottom" as a valve calculated to resist liquids exerting pressure on the concave side. From the left auricle Gad caused water to pass out of the right and left ventricular walls, but, as the auricular openings have no valves, this only serves to emphasize the extensive canalization which the Thebesian system represents. The system might, therefore, be considered as essentially calculated to distribute venous blood from the right auricle to the entire heart: a fact which the free anastomosis with the venous channels would seem to sustain.

Pratt states that he has seen "structures accessory to these *ventricular* foramina which might in any way serve the office of valves" . . . "the edge of the foramen is usually sharply defined and may frequently exist as a partial, *shelf-like*, covering, giving the impression perhaps of an attempt at a membranous valve; but it is seldom more than this." A shelf means a projection, and the fact that it is membranous suggests that during ventricular *contraction* this valve is pressed against the opening and closes it: a feature which involves the possibility that during diastole a current—whether venous or arterial—flows into the ventricle through its foramina. That the latter and their valves open inwardly—*i.e.*, in the ventricle—is demonstrated by Pratt's experiment, in which he injected the coronary *veins* with starch and celloidin and found that even these passed *into* the ventricle. If, therefore, the venous blood of the right heart at all enters the muscular *walls* it is not through the foramina of the ventricle, *i.e.*, from below; it must be through the openings above, *i.e.*, those in

the right auricle. The experiment in which the cannula was tied in the pulmonary artery, the blood being "allowed to enter the right auricle through insufficiency of the tricuspid," appears to us to further sustain this fact. The heart continued "its rhythmic contractions for eight hours: a period considerably in excess of that observed in nutrition through the vessels of Thebesius alone. It was inferred that blood had gained access from the auricle to the coronary veins and had thus aided materially in the nutrition." While this course may have been taken by some of the blood in the experiment, it is obviously not a normal one during life, and the unusual duration of the contractions seems to us to indicate that the blood that penetrated into the right auricle found its way into the Thebesian system *via* the openings in this auricle, thus approximating as nearly as possible normal conditions.

The relations between the coronary veins and the Thebesian channels are self-evident, excepting, however, a theoretical back-flow from the auricles into the veins suggested by Pratt, which appears to us abnormal; at least it is not compatible with our views of the process. The Thebesian vessels and coronary veins were found to communicate freely on the right side, but not on the left, with the ventricular foramina. The septal foramina were also found to communicate with the coronary vein at the end of the sinus. An interesting feature is the fact that blood passed into the right ventricle flowed freely from a cut vein of the *left* heart (experiment of April 3, 1897). On the other hand, the relations between the coronary arteries and the Thebesian vessels are of a peculiar kind; thus the communication between the *left* coronary artery and the *right* ventricle seems as free as that between the same artery and the *left* ventricle (through the Thebesian channel) is limited. The experiment in which a colored solution was passed into the left coronary artery caused an accumulation of 400 cubic centimeters to flow from the right ventricle, while only 4 cubic centimeters flowed from the left, sufficiently emphasizes this fact. Haller, who had observed that injected substances flowed out freely from the surfaces of both ventricles, states that "the passage from the arteries into the cavities of the left side is more difficult."

All these features seem fully to supply the needs of the function with which the secretion of the suprarenal glands must be connected, if the phenomena witnessed in many disorders and after the use of most remedies have been correctly interpreted. That we are in the presence of a dual process of which the suprarenal secretion, operating in the right heart, and the arterialized blood in the left heart are active factors seems probable. Again, the marked power of arterial blood—or rather of plasma—since the defibrinated blood filtered through cotton was used—to sustain functional activity, even when only poured into the ventricles, as shown by Pratt, certainly indicates that the blood must alone be able, during life, to compensate, in case of need, for insufficiency of blood furnished by the coronary arteries.

The contractions of the *left heart* seem to me to be greatly assisted by the arterial blood that enters it, and mainly by that which enters the cavities themselves. The experiments of Pratt having shown that contraction could be produced by contact with arterialized blood, the arrival into the *auricle* of a normal quantity of this fluid must be fully capable, therefore, of causing contraction of the walls of that cavity. The relations of the several structures and the mechanism involved are in all probability as follows: The main structures upon which the arterial blood reacts are (1) the *musculi pectinati* and (2) the *sinus venosus* and *appendix auriculæ*, all of which are so disposed as to offer as much surface as possible to the blood. The walls of the cavities mentioned are provided with numerous channels, the Thebesian “veins,” to satisfy this purpose. The blood which enters the *auricle* when it is dilated penetrates all the circuitous areas around the *musculi pectinati* and into the Thebesian vessels, and the ensuing contraction forces the blood-plasma into the smaller subdivisions of these vessels, from which they find their way into the *auricular veins*. When the arterial blood reaches the *ventricle*, a process similar to the preceding occurs. The *columnæ carneæ* are disposed so as to offer considerable surface to the blood, while the ventricular walls are permeated with Thebesian channels, into which the blood penetrates during *diastole*. The contraction induced closes the apertures of these channels, and forces the blood-

plasma into their smaller ramifications and finally into the veins. The larger channels carry the corpuscular elements to the latter. The rôle of the coronary arteries will be referred to later on.

The *right heart*, as I view the process, owes its functional activity mainly to the suprarenal secretion brought to the cavities by the vena cava. I have sufficiently emphasized the power of this agent to restore cardiac action and sustain it even when the entire spinal cord has been obliterated. The manner in which it exercises its powers is similar to that of the arterial blood on the left side. On penetrating the auricle the contractile structures are submitted to its immediate effects; but the orifices of the Thebesian vessels or channels are more numerous and larger than in the left auricle. The membranous edges previously referred to as valves by the investigators quoted do not appear to me to merit being considered as such after careful examination of these structures in the ox-heart. The aperture being closed by the least squeezing of the tissues containing them, it seems evident that they should as readily close under the powerful contraction of the auricular tissues. The right ventricle also presents a very much larger number of Thebesian orifices than the left, while its walls, though thinner, plainly show the ramifications of these channels. That the venous blood charged with suprarenal secretion should at once penetrate the latter when the ventricle begins to contract is self-evident. Return of the blood to the circulation is effected in the same way as in the case of the left heart: *i.e.*, through the coronary veins.

The whole process is an exceedingly uncomplicated one, but, as we shall see later on, it simplifies many obscure problems, while affording, in connection with the coronary arterial blood, a supply in keeping with the vital importance of the organ itself. Again, Dr. Pratt's experiment, in which blood injected into the *left* auricle flowed freely from the right ventricle, emphasized the possibility of compensation in case of need. Thus, while under normal conditions, the pressure in both ventricles must be equal, reduced contraction—of the right ventricle, for example—through insufficiency of the adrenals would automatically cause the arrival into it, through

the Thebesian foramina of the septum, of at least some arterial blood. That this does not always suffice to maintain inter-ventricular equilibrium, however, is illustrated by the dicrotic pulse, the pulsus paradoxus, and kindred phenomena.

Suggestive in this connection are the remarks of Professor Porter in his review of the subject of cardiac innervation in the "American Text-book of Physiology": "A positive demonstration that the nerve-cells in the heart are not essential to its contractions," says this observer, "is secured by removing the tip of the ventricle of the dog's heart and supplying it with warm defibrinated blood through a cannula tied into its nutrient artery. Long-continued, rhythmical, spontaneous contractions are thus obtained (Porter¹⁰). As the part removed contains no nerve-cells, the observed contractions can only arise in the muscular tissue, provided we make the (at present) safe assumption that the nerve-fibers do not originate impulses capable of inducing rhythmic muscular contractions." In other words,—and this may be said to apply to all muscular elements including those of the muscular coats of the stomach and intestines,—the cardiac muscle is endowed with the inherent power to contract, even small detached pieces, when placed in appropriate media being capable of doing so. In the body, indeed, this contractile power is merely, so to say, kept active, and Porter remarks—almost prophetically in the light of our views: "The demonstration that the nerve-cells are not essential to contraction places us one step nearer the true cause of contraction. It is some agency *acting on the contractile substance*.¹¹ Evidence is accumulating that this agent is a *chemical substance*, or substances, *brought to the contractile matter by the blood*."

That the "chemical substance brought to the contractile matter by the blood" is represented by the adrenal secretion and the oxidizing substance seems clear. Brown-Séquard over fifty years ago urged that the inferior vena cava contained *some* undetermined substance which contributed to the heart's dynamism.

⁹ Porter: "American Text-book of Physiology," second edition, 1900.

¹⁰ Porter: Journal of Experimental Medicine, vol. II, p. 391, 1897.

¹¹ All italics are our own.

THE ACTION OF THE ADRENAL SECRETION AND THE OXIDIZING SUBSTANCE UPON THE CARDIAC MUSCLE.

The histology of the myocardium still offers a broad field for conjecture, notwithstanding the many investigations to which it has been submitted by modern observers. The known facts are briefly these: Its tissue is composed, in man, of short, round fasciculi, or bundles, of striated fibers, possessed of thick lateral projections. The latter directly connecting with a similar projection of the adjoining bundles and being cemented to it, a thick close-meshed net-work is formed: a characteristic of the heart-muscle. But it differs from other muscles in several other particulars; its fibers are one-third smaller and their striæ are much more faint; they possess no sarcolemma and are, therefore, exposed to the immediate action of any fluid that may surround them. The manner in which the contractile structures are combined in bundles is also peculiar: each bundle is made up of central prismatic fasciculi of round fibers, in which nuclei (one or two) with their surrounding protoplasmic area are imbedded, the whole being surrounded with flat or ribbon-like columns of muscle-fibers. The perinuclear protoplasm referred to generally contains fat-droplets and *minute pigment-granules* which resemble haemoglobin, and sends projections between the surrounding muscular fibers so that each of the latter is connected with and is only separated from its neighbor by a layer of protoplasm. This arrangement does not in any way modify the manner in which the sarcous elements are disposed, while the disks, clear spaces, etc., are precisely as they are elsewhere in the organism. These muscular "primary" bundles form, by their union with one or two of their neighbors, columns, or chains—or "secondary" bundles, which are covered, as shown by Ranvier, with a sheath of loose connective-tissue cells, which cells, in turn, connect with one another by numerous projections, or extensions. The primary fasciculi also contain connective-tissue sheaths which invest the muscle-fibers and are likewise supplied with connective-tissue cells. All this forms a close, though permeable, net-work, which makes it possible for a liquid to penetrate the muscular columns or chains and come into direct contact with the bare, or exposed, muscle-fiber.

Indeed, the intimate structure of the myocardium precisely supplies the required structure for the equable and free distribution of such an agency as the suprarenal secretion represents. Fluids can penetrate through the maze of cellular tissue to the bare muscular fibers; the sheaths that include the columns or chains of muscular bundles afford a peculiar system of canalization through which the liquids can easily gain access to them. These canals—the lacunæ of Henle—are the intervals between the columns of secondary bundles, or their sheaths, rather, which are placed in longitudinal apposition. Schweigger-Seidel and Ranvier having observed that interstitial injections of colored substances penetrated the lymphatic vessels, the lacunæ have been considered as adjuncts, or extensions, of the latter.

Renaut,¹² however, concluded that the penetration of the colored fluids into the lymphatics merely demonstrated the weak resistance of the endothelial coat of the latter, and the spaces, or lacunæ, of Henle being unprovided with endothelial walls, there was no ground for the prevailing belief that they represented lymphatic vessels. He found that all the lymphatic capillaries of the myocardium are located on the surface of the heart underneath the pericardium. They are large and bosselated and form a mesh-work which covers the whole cardiac surface, and send smaller blind pouches into the muscular interstices. The spaces of Henle should be considered, he thinks, “not as true lymphatic cavities analogous to those observed around the pulmonary lobules of certain animals, but as mere connective-tissue spaces, which represent, in fact, pathways for lymph.” In a foot-note Berdal states that the spaces of Henle are crossed by “vessels,” and in the text the following remark as to the identity of this lymph appears: “The muscular fibers of the heart are thus bathed in connective-tissue spaces in which lymph easily circulates; but this lymph is not that of the lymphatic vessels or capillaries, but that of loose connective-tissue spaces (Renaut).” It is needless to state that this suggests the presence of blood-plasma. Still, we can only consider this deduction as tentative.

¹² Renaut: *Traité d'Histologie pratique*, p. 719; quoted by Berdal, *loc. cit.*, p. 825.

The manner in which the blood-plasma, whether venous or arterial, is distributed by the Thebesian channels is well shown in a study of the vessels of the heart by Arthur V. Meigs.¹³ The extreme paucity of literature on the Thebesian channels has caused them to be overlooked by practically all histologists; that they should be treated as capillaries in the author's paper is, therefore, as normal as it is for text-books to do so. "The capillaries of the human heart," says Dr. Meigs, "differ in two ways from those of other parts of the body: they penetrate the muscular fibers, and some of them are larger than those found elsewhere, and of different arrangement. . . . The accompanying illustrations are drawings which were made with the camera lucida. They are from sections of two human hearts. The first is from the heart of a negro woman, 40 years old, who died of burns. Some pieces of the organ were preserved in Fleming's solution, and others in 70-per-cent. alcohol, and they were stained in bulk with borax-carmin and imbedded in paraffin. The second heart is that of a man, 30 years old, who died of lead encephalopathy. When the post-mortem examination was made, the heart being still quite fresh, there was injected through each of the two coronary arteries as much as the blood-vessels would easily receive of a solution of 3 grammes of Berlin blue (Grübler's) in 600 cubic centimeters of water. Pieces of the organ of suitable size were at once placed in preservative fluid, some in 70-per-cent. alcohol, and others in formaldehyde solution. The tissue was afterward stained in bulk with borax-carmin and imbedded in paraffin.

"The penetration of the muscular fibers by the capillaries is made perfectly clear by the illustrations; it is shown as well by the injected as by the uninjected heart. The two methods of demonstration supplement one another, because, in injected tissue which has been stained, the blood-vessels and their situation are made very obvious by the contrast of color, but the details of the structure of the walls are obscured by the injection material, while, on the other hand, in the uninjected tissue, the structure of the blood-vessels can be seen with the utmost distinctness. In Figs. 1 to 4 the capillaries are easily recog-

¹³ Arthur V. Meigs: *Journal of Anatomy and Physiology*, Jan., 1899.

nized. Their situations in relation to the muscular fibers are very varied. Some are in the intermuscular fibers, others slightly indent the sides of the fibers; still others are within the fibers close to their peripheries, and sometimes the capillaries are in the very centers of the fibers. This penetration of the muscular fibers of the human heart in the adult is a most

DESCRIPTION OF DR. MEIGS'S PLATE.

The amplification has been reduced about one-third in the reproduction herein presented.

"Fig. 1.—x 420. From a man, 30 years old, who died of lead encephalopathy. A section of papillary muscle of the heart cut across the fibers. *bb* are injected capillaries, the one partially and the other entirely within the muscular fibers. *c*, A capillary which remains uninjected; its nucleus is included.

"Fig. 2.—x 420. From the same tissue as Fig. 1. *v*, A vein stained by the injection material. *bb*, Capillaries whose precise situation cannot be defined. They cannot be said to be intermuscular spaces, nor to be entirely within fibers. The effect is as if the fibers were coalescing.

"Fig. 3.—x 420. From the same tissue as Fig. 1. *f*, A capillary in a fiber. *g*, A capillary in the center of a very small fiber. This is perhaps the most convincing instance of the penetration of a muscular fiber by a capillary.

"Fig. 4.—x 420. A section of heart cut transversely to the muscular fibers, from a negro woman, 40 years old, who died of burns. The muscular fibers are of irregular shape. *d*, A capillary within a muscular fiber, its nucleus upon one side producing a resemblance to a seal ring. *e*, A capillary within a muscular fiber. *f*, A capillary in an intermuscular space; its nucleus being included, it resembles a seal ring. *g*, A capillary in an intermuscular space; its endothelial wall appears as a simple circle.

"Fig. 5.—x 115. From the same tissue as Fig. 4. A large capillary, receiving many branches and surrounded by muscular tissue. The capillary and its branches are almost filled with blood-corpuscles. The capillary walls are distinctly visible, containing many flattened endothelial nuclei.

"Fig. 6.—x 42. From the same tissue as Fig. 1. Not printed in two colors, because the essentials show equally well in black. *m*, Muscular tissue. *a*, An arteriole; the solid black within its caliber is injection material. *v*, The accompanying vein to the arteriole, *a*; it also contained a little of the injection material; these two vessels are in a connective-tissue interspace. *c*, A large capillary; it contains a good deal of the blue injection material, which is represented by the heavily-shaded portions. These three vessels—arteriole, vein, and capillary—give a good idea of the character of such vessels in the heart. The great size of the capillary is the most striking feature."

striking and curious phenomenon, and it does not exist at an early embryological stage. The condition is, therefore, one of later development, but it is not yet known at how early an age it does exist

"Very large capillaries are found in the human heart, and such vessels are shown by Figs. 5 and 6. It is not common to find minute veins in company with the arterioles in the deepest

Fig. 1.



Fig. 2.



Fig. 3.

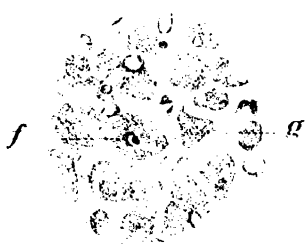


Fig. 4.



Fig. 5.



Fig. 6.



portions of the muscular substance of the heart, although it is well known that, upon the surface and in the connective-tissue interstices, arteries are found with their venae comites, just as they are in other organs and tissues. The arrangement of the vessels upon the surface and in the interstices is in marked contrast with that found in the muscular substance proper. Here, when an arteriole is accompanied by an efferent vessel, this vessel is single coated and composed of endothelium, being exactly like the smallest capillaries, except in size. These peculiar large capillaries are found not only in company with arterioles, and, therefore, when carrying on the function usually performed by veins, but also alone. When they are alone, it is impossible to be certain whether their function was afferent or efferent. It may well be that arterioles are less numerous in the heart than in other tissues, and that their place is taken by the large capillaries. These capillaries are so numerous and of such size that it seems likely they perform the function of reservoirs. The presence of the large capillaries and the penetration of the muscular fibers by the capillaries indicate a provision for the blood-supply of the heart even more bountiful than that of the other organs."

That these vessels are the Thebesian channels is evident; their mode of distribution and the peculiar endings of their subdivisions is particularly well shown in Fig. 6, while the outpouring of plasma for absorption by the muscle-elements is suggested by Fig. 5.

The fact that the distribution of the Thebesian channels is analogous to that observed in the heart of the frog has, we have seen, been noted by Pratt. This had also been noticed by Lannelongue, but this author considered the channels of the human myocardium as vestiges of the batrachian system. Bernal, who alludes to the latter, states that in the frog and in the batrachian *urodela* there are no ordinary blood-vessels. "The muscular fasciculi intercept cavernous spaces into which the blood penetrates directly and from which they are only separated by endothelium. *The frog's heart is thus a true sponge the structures of which, formed of muscular fibers, nourish themselves by imbibition.* In mammals, on the contrary, the myocardium contains distinct vessels. The capillaries form a net-work the

meshes of which, elongated and parallel to the muscular fasciculi, are connected by short branches, which give each mesh the appearance of a parallelogram. When these vessels cross the spaces of Henle, they are covered, on the external surface, with flat connective-tissue plates." Pratt's observation not only includes the analogy between the human lung and that of the frog, but also with that of the cat, a mammal. Under these conditions, it becomes clear that in man, also, *the heart-muscle may be regarded as a sponge-like structure, the contractile elements of which are nourished and supplied with working energy by substances in the blood-plasma.*

What is the rôle of the blood of the coronary arteries in the functions of the heart? This may perhaps be traced by analyzing the effects of ligation of these arteries upon these functions. Porter¹⁴ refers as follows to the experimental work in this connection: "The frequency of arrest after ligation is in proportion to the size of the artery ligated, and hence to the size of the area made anæmic, and is not in proportion to the injury done in the preparation of the artery. The circumflex and descendens may be prepared without injuring a single muscle-fiber, yet their ligation frequently arrests the heart, while the ligation of the arteria septi, which cannot be prepared without injuring the muscle-substance, does not arrest the heart. It is, moreover, possible to close a coronary artery without mechanical injury. Lycopodium-spores mixed with defibrinated blood are injected into the arch of the aorta during the momentary closure of that vessel and are carried into the coronary arteries: the only way left open for the blood. The lycopodium-spores plug up the finer branches of the coronary vessels. The coronary arteries are thus closed without the operator having touched the heart. Prompt arrest, with tumultuous fibrillary contraction, follows."

If the plasma that reaches the heart by way of the Thebesian channels can sustain both its nutrition and its contractions, how can such results as these be accounted for? The sudden arrest of the heart's action by plugging the coronary arteries certainly points to a predominating function, and, more than this, to a function of which they are alone the sources of blood-

¹⁴ Porter: *Loc. cit.*

supply. That the rôle of the coronary blood is precisely that which obtains elsewhere in the organism is forcibly suggested by the experiments of Langendorff, who was able, according to Porter, "by circulating warmed *oxygenated defibrinated* blood through the coronary vessels, to maintain the hearts of rabbits, cats, and dogs in activity after their total extirpation from the body." It is clear that the blood-plasma can incite functional activity when introduced through the coronaries as well as when introduced into the ventricles. "Even pieces removed from the ventricle will contract for hours," continues the author, "if fed with blood through a cannula in the branch of the coronary artery which supplies them (Porter¹⁵). It is evident, therefore, that the cause of the rhythmic beat of the heart lies *within the heart itself*, and not within the central nervous system."

The italicized words represent precisely the factor of the problem which must be eliminated to enable us to differentiate the rôle of the coronary plasma from that of the Thebesian plasma, for blood will not alone induce contraction of the cardiac walls; almost any irritant will under appropriate conditions. Indeed, in the latter case it will sometimes undergo contractions without any external irritation; thus, "a strip of muscle cut from the *apex* of the tortoise ventricle and suspended in a moist chamber begins in a few hours to beat apparently of its own accord with a regular, but slow, rhythm, which has been seen to continue as long as thirty hours. If the strip is cut into pieces and placed on moistened glass slides, each piece will contract rhythmically. Yet in the apex of the heart no nerve-cells have been found" (Porter). Hence the power to contract is inherent in the contractile tissues, and subject, as elsewhere in the organism, to exacerbations of activity under appropriate stimulus. This fact being now established, our inquiry is simplified, since we need only to inquire into the nature of the processes through which it is utilized.

Analysis of the requirements of the right heart soon reveals the fact that the muscle-fibers require the same blood-supply that any muscle of the body does. Indeed, we then realize that the coronary arteries are their only source of oxy-

¹⁵ Porter: *Journal of Experimental Medicine*, vol. II, p. 391, 1897.

gen. The venous blood that reaches it through the Thebesian channels has been depleted of this gas by the rest of the organism, and the suprarenal secretion, owing to its marked avidity for it, must, while in transit through the inferior vena cava, have deprived it of the little that might have remained in loose combination. We have reviewed the ultimate distribution of the coronary arteries as given by Berdal. It does not differ from that of other text-books. These generally concur in stating that the larger branches are distributed to the connective tissue between the large fasciculi, and once therein divide into arterioles, which, in turn, subdivide into capillaries that entwine the primary muscle-fasciculi. "The capillaries of the myocardium are very numerous," say Böhm and von Davidoff, "and so closely placed around the muscle-bundles that each muscular fiber comes in contact with one or more capillaries." Do they serve here, as elsewhere, to supply the muscle-fiber with its *source of energy*—*i.e.*, the carbohydrates that enter into the formation of the myosinogen—besides furnishing the oxidizing substance which sustains the combustion processes when brought into contact with this myosinogen? This is precisely where a difference between the muscular functions of the heart and those of other muscular structures appears to us to exist.

There is practically no *passive* period in the heart's action when we consider that its stage of *activity* recurs every three-fourths of a sound; and the formation of myosinogen in its contractile elements, were it to proceed as slowly as it does elsewhere, would seem totally inadequate. Still, if the coronary blood is not endowed with the mission of supplying the heart-muscle with its source of energy, we are relegated to the venous blood of the Thebesian vessels and its suprarenal secretion for the myosinogen-forming products. A possible source of energy suggests itself when we consider that a carbohydrate known to react under the effects of the oxidizing substance is present in the hepatic veins,—*i.e.*, dextrose,—and that this sugar must pass through the right heart. As is well known, these veins carry their sugar to the inferior vena cava. That it is not used by the heart, however, was shown by a careful analysis of the whole question. This is submitted in the twelfth

chapter. For reasons submitted in the second volume I was led to conclude that the minute granules referred to on page 433 were actually supplied to the heart through the intermediary of leucocytes. These cells were found to migrate from the liver (also through the hepatic veins) to the inferior vena cava, where they meet the adrenal secretion and proceed with it to the right ventricle. The evidence seems incontrovertible. The subject is so far-reaching, however, that it had to be considered separately. I shall, for the present only, refer to these granulations as "granules β " (Ehrlich). We now have, it seems to me, the elements necessary to account for the functional phenomena witnessed, namely:—

1. *The adrenal secretion, to contract the right auricle and ventricle and thus insure the penetration of the Thebesian blood into the cardiac walls (which contraction venous blood or its contained granules β would not cause).*

2. *The granules β , to account for the unusual and continuous production of energy which the heart converts into work.*

3. *A continuous supply of oxidizing substance via the coronary arteries to insure the combustion processes through which this energy is liberated.*

The annexed colored plate shows the manner in which the adrenal secretion and the granules β simultaneously reach the right auricle.

We can now understand why plugging of the coronary arteries should, as stated by Porter, arrest cardiac action. Referring to the effects of embolism and thrombosis of these arteries, this investigator also says: "That part of the heart-wall supplied by the stopped artery speedily decays. The *bloodless area* is of a dull-white color, often faintly tinged with yellow; rarely it is red, being stained by *hæmoglobin* from the neighboring capillaries. The cross-section is *coarsely granular*. The nuclei of the muscle-cells have lost their power of staining. The muscle-cells are dead, and connective tissue soon replaces them. This loss of function and rapid decay of cardiac tissue would not take place did anastomosis permit the establishment of collateral circulation between the artery going to the part and neighboring arteries. . . . The objection that one of the coronary arteries can be injected from another, and that,

therefore, they are not terminal, is based on the incorrect premise that terminal arteries cannot be thus injected, and has no weight against the positive evidence of the complete failure of nutrition following closure." As I interpret the process, the absence of anastomosis further suggests the existence of an additional source of energy; but the cardiac arrest after ligation of the coronary also indicates that compensation from the opposite heart can only be gradually established. On the whole, the coronaries of the right side are as important as if they alone supplied the needs of the functions of that side. The granules β and the adrenal secretion are furnished to compensate for the absence of *arterial* blood in the right auriculo-ventricular cavities and in their Thebesian channels; but, the right coronaries being the only source of one of the three *necessary* factors of the process, their obliteration means as much as that of the left coronaries does to the left heart.

We can also understand why the contractile elements of the primary fasciculi are bare. They are constantly bathed in the plasma from which they obtain the granules β that enter into the formation of their myosinogen. The absence of oxygen in this fluid renders it perfectly harmless to the delicate structures that surround the primary and secondary bundles of muscle-fiber, and to the net-works of arterial capillaries that hug the bare fibers. The latter, by a rapid absorption,—which the presence of sarcolemma would counteract,—are constantly forming their products of metabolism: *i.e.*, myosinogen. The arterial capillaries, "coated, on their external surface, with flat connective-tissue cells" (Berdal), when they cross the spaces of Henle, being the only carriers of oxygen, normally become the active factors of nutrition and function. Their blood is the normal excitant—as elsewhere. The venous blood brings the granules β ; the adrenal secretions, by contracting the cardiac walls, forces it into the Thebesian channels; the bare muscle-fibers absorb the granules and convert them into their own particular kind of fuel, myosinogen; the capillary blood supplies the energy for this metabolism—oxygen—and simultaneously sustains, again with its oxygen, the combustion processes upon which the continuous work of the organ depends. Here, as elsewhere, the potential energy of

the chemical agencies present becomes converted into mechanical energy, which manifests itself as visible motion.

The left heart—the coronaries of which are larger than those of the right—presents anatomical features which modify, in a measure, the manner in which its physiological functions are performed. Both its auricle and ventricle containing arterial blood fresh from the heart, the Thebesian circulation does not appear to fulfill the primary rôle it does in the right heart. Indeed, the various experiments of Pratt and his predecessors and my own careful examination of the ox-heart distinctly show that the Thebesian circulation of the left heart, as regards intraventricular orifices, is much less important than that of the right heart. Still, the evident permeability of the inter-ventricular septum and the histology of the left myocardium suggest that the left heart must receive material aid from the adrenal secretion and its granules β . This feature will again be referred to in the twelfth chapter.

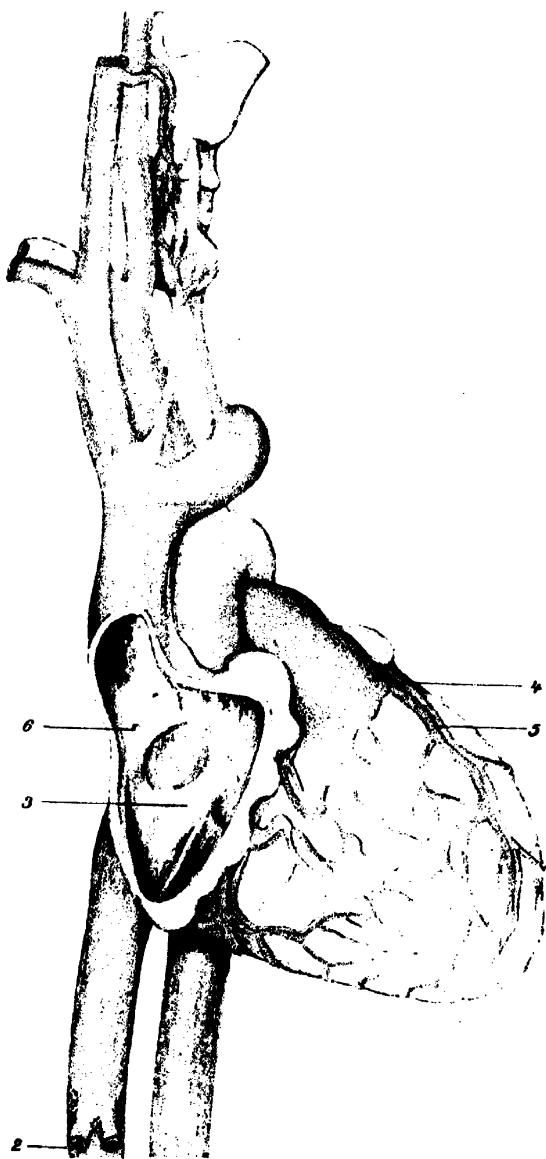
A feature that may be considered as demonstrated, and common to both sides, is the return of the blood, whether its source be the Thebesian or coronary systems, by way of the coronary veins. We have seen that Langer expressed the opinion “that the foramina Thebesii in the ventricles communicate with the veins by capillaries alone.” My conception of the process involved would necessitate such an arrangement as regards the right heart. Indeed, so direct is this connection that even such viscid substances as starch and celloidin were found by Pratt, when introduced into the coronary veins of the ox, to emerge from the foramina Thebesii. Still, we could hardly expect such a free transit on the left side of the organ, inasmuch as the presence here of arterial blood only would suggest the presence of a structural organization similar to that of ordinary muscles. Indeed, referring to the vascular connections of the left heart, Pratt says: “So intimate a connection, however, between the coronary veins and the vessels entering the left ventricle I have not yet been able to demonstrate.” Again, on the right side the connection with coronary veins must evidently be a physiological one, since “a small, but steady, stream of venous blood issued from them” when the veins were incised after the right ventricle had been filled with defibrinated blood.

But "no flow of blood occurred from the artery, although there was a free escape from an incision in an accompanying vein" in an experiment similar to that previously referred to, also performed by Dr. Pratt. In fact, it appears to me very doubtful whether even the capillary communication between coronary arteries and the Thebesian vessels, referred to by the latter observer in his conclusions, at all exists—at least in the walls of the right heart. Even disregarding my views, it seems evident that the admixture of venous blood with the arterial blood would greatly reduce and perhaps annul the functional efficacy of the latter as an oxidizing agent.

We can now understand how the adrenal secretion so greatly influences cardiac activity. An increase of it augments the force of the contraction, but the heart does not dilate as promptly nor perhaps as completely; hence its action is slower, but more forcible; we have seen that this represents the primary effect of all drugs sufficiently active to stimulate the adrenals. A still greater quantity of adrenal secretion increases the violence of cardiac action; the vessels are tense, and ecchymoses, hæmaturia, epistaxis, etc., may ensue. The heart acts normally, however, in the sense that its diastole is almost complete. Continuous cardiac stimulation through excessive production of adrenal secretion, due in turn to excessive production of iodothyryn, as in exophthalmic goiter, causes the heart to contract before it has exhausted its complete diastole and to work within a narrower field. Its contractions are sharp, but rapid: the type of the "cramped heart." Increase of adrenal activity involves increase of oxidizing substance; hence the left heart is correspondingly stimulated. When, however, adrenal insufficiency occurs, the phenomena follow an opposite course; when total inhibition of the adrenal system ensues, the vascular walls, losing all their functional stimuli,—the adrenal secretion, the granules β , and the oxidizing substance,—gradually cease their contractions and lapse into diastole.

THE INNERVATION OF THE HEART.

We are again brought, by analysis, to the realization that the efferent nerves distributed to the heart *incite* and *govern* functional activity but contribute nothing to the continuation



MECHANISM OF CARDIAC ACTION. [*Sajous.*]

1, Inferior Vena Cava, the blood of which contains Adrenal Secretion. 2, Hepatic Veins, the blood of which contains granules β derived from the Liver. 3, Right Auricle. 4, One of the Coronary Arteries. 5, One of the Coronary Veins. 6, One of the Foramina Thebesii.

of vital processes *per se*. Indeed, in the heart they do naught else than in other parts of the organism. One set of nerves distributed to the cardiac arteries provokes dilation to increase cardiac activity; another set causes constriction of these vessels when cardiac activity is to be reduced. "The rich nervous supply of the heart is derived from the coronary *plexuses*," says Piersol, "and includes numerous medullated fibers coming from the *pneumogastric* as well as the non-medullated *sympathetic* fibers proceeding from the cervical ganglia. Numerous microscopical ganglia are found along the course of the large nerve-trunks accompanying the branches of the coronary arteries, especially in the longitudinal interventricular and in the auriculo-ventricular furrows. Many additional small groups of ganglion-cells occur within the muscular tissue associated with the fibers supplying the intimate structure." Briefly, according to prevailing teachings the vagus and sympathetic are the nerves which govern the functions of the heart.

Is this true? In the light of my own views, it is subject to doubt; and, precisely as I have shown it to be the case with the kidneys, all the nerves supplied to the heart belong to the sympathetic system.

ACCELERATION.—Legallois, early last century (1812) urged that the nerves which increased the beats of the heart in a given time belonged to the sympathetic system. Although vigorously attacked by Bezold and others, this doctrine has steadily gained ground, and most investigators, including Heidenhain, Langley and Gaskell have accepted Legallois's view. It becomes a question, however,—in the light of my views,—whether acceleration represents the motor phase of cardiac action, and therefore, whether or not as in the kidney, the sympathetic fulfills the rôle of motor, *i.e.*, of vasodilator nerve. That it does is shown by the experiments of E. and M. Cyon¹⁶ who found that occlusion of cardiac vessels did not cause acceleration—in other words that it was not by *reducing* the blood supplied to the heart walls that the accelerators acted upon the heart. On the other hand, as will be shown under the next heading, constriction of the cardiac arteries, *i.e.*, dimi-

¹⁶ E. and M. Cyon: *Archiv f. Physiol.*, 1867.

nution of the blood supplied to the cardiac muscle, slows the heart's action. Indeed, Baxt¹⁷ observed a distinct antagonism between the vagi in the neck—owing as shown below to the presence of cardiac vasoconstrictor fibers in this nerve—and the accelerators, when stimulated simultaneously. The vagi suppressed the accelerators invariably, in fact, and irrespective of the strength of the current. It is evident, therefore, that acceleration is not due to constriction of the cardiac arteries, and that the sympathetic accelerators must act upon the heart by producing dilation of these vessels.

The vasodilator properties of the accelerators have, in fact, so legitimate a claim to recognition that in his recently published review of our knowledge on the subject Carvallo¹⁸ remarks: "The first thoracic ganglion, or stellate ganglion seems to contain vasodilator fibers which almost always cause augmentation of speed." He forcibly illustrates this fact by a table demonstrating that the vessels so influenced show *an increased blood-flow in a given time*, when the accelerator nerves are stimulated, and closes his review with the following words: "We may conclude therefore that the heart possesses a complete vasomotor apparatus the vasoconstrictor fibers of which reach it essentially by way of the vagus, and the vasodilator nerves by the stellate ganglia [first thoracic] and the annuli of Vieussens."

Briefly, "acceleration" represents an exacerbation of activity of the heart, and just as we found such increased activity produced by vasodilation and the admission of an excess of blood, in other organs, so do we find it here.

INHIBITION.—In the light of foregoing statements, this phenomenon should assert itself as a result of excessive constriction of the cardiac arteries and diminution of the blood supplied to the cardiac muscle. That such is the case suggests itself from various directions.

The inhibitory effect of excessive constriction of the coronaries is beyond question. Chirac¹⁹ found that the beats of a dog's heart were soon arrested when one of the coronaries was

¹⁷ Baxt: Arb. a. d. phys. Anst., Leipzig, 1875.

¹⁸ Carvallo: Richet's Dictionnaire de Physiol., p. 347.

¹⁹ Chirac: "De Motu Cordis," p. 121, 1698.

tied. Erichsen²⁰ observed a similar result after tying these vessels. Leonard Hill²¹ referring to the investigations of Cohnheim and Schulthess-Rechberg,²² McWilliams,²³ Bettelheim,²⁴ and others, also states that "ligaturing one of the large branches only is frequently sufficient to cause arrest." Again, Sée, Bochefontaine and Roussy²⁵ observed that substances capable of plugging the coronaries—lycopodium spores, for instance—also caused cardiac arrest. Porter²⁶ plugged the left coronary artery in nineteen dogs and says that "the closure of the artery was always promptly followed by arrest." As the result of closure by ligation in sixty-seven dogs, he reached the deduction that "the frequency of arrest is in proportion to the size of the artery ligated." As cardio-inhibitory impulses transmitted through the vasoconstrictors of both vagal trunks probably influence *all* the cardiac arterioles simultaneously, the ease with which the heart's action can be arrested by exciting the bulbar center is easily accounted for. Finally Kolster,²⁷ Porter,²⁸ and others have shown experimentally that the part of the heart supplied by an infarcted coronary artery degenerates.

Yet, if the vasomotor impulses inhibit the heart by causing excessive constriction of the coronaries and their offshoots, the effects on the heart wall must coincide with those resulting from deprivation of blood. Such is undoubtedly the case: E. Weber²⁹ observed that during partial inhibition the cardiac contractions were weakened, while Schiff³⁰ found that the muscular elements of the entire organ responded less or not at all to stimuli. François-Franck, Fischel,³¹ and others observed that the cardiac walls were softer than usual. Foster³² states

²⁰ Erichsen: London Hospital Gazette, vol. II, p. 561, 1842.

²¹ Leonard Hill: Schäfer's "T. B. of Physiol.," vol. II, p. 1, 1900.

²² Cohnheim and Schulthess-Rechberg: Virchow's Archiv, Bd. lxxxv, H. 3, S. 503, 1881.

²³ McWilliam: Jour. of Physiol., vol. VIII, p. 296, 1887.

²⁴ Bettelheim: Zeit. f. klin. Med., Bd. xx, S. 436, 1892.

²⁵ Sée, Bochefontaine and Roussy: C. R. de l'Acad. des sci., T. xcii, p. 86, 1881.

²⁶ Porter: Jour. of Exper. Med., vol. I, p. 46, 1896.

²⁷ Kolster: Skandinav. Archiv f. Physiol., Bd. IV, p. 1, 1893.

²⁸ Porter: Pflüger's Archiv, Bd. IV, Hft. 7 u. 8, S. 366, 1894.

²⁹ E. Weber: "Handwörterbuch d. Physiol., Bd. II, S. 42, 1846.

³⁰ Schiff: Archiv f. Physiol. Hellk., 9ter Jahrgang, S. 22, 1850-51.

³¹ Fischel: Archiv f. exp. Path. u. Pharm., Bd. xxxviii, Hft. 3 u. 4, S. 228, 1897.

³² Foster: "T. B. of Physiol.," sixth American edition, Phila., 1895.

that when the interrupted current is used to stimulate the vagal trunk, the heart remains in diastole, motionless and flaccid. When, however, the current is weak, the beats are only slowed and weakened. Coats³³ ascertained manometrically that the contractions were markedly reduced in force. Gaskell³⁴ and Stefani³⁵ found that the ventricular tonicity was reduced. Muskens³⁶ also found that stimulation of the vagus lessened the force of the contraction in the frog.

Gaskell³⁷ characterizes as "most striking" the attending *depression of activity*. Still, there is no loss of inherent muscular irritability, since, according to Foster,³⁸ a pin prick in the heart during inhibition may cause the organ to resume its beats; the morbid phenomena are, therefore, the result of a deficient supply of the nutrient components of the blood. Porter³⁹ states that "but little is known as to the constituents of the blood which are essential to the life of the mammalian heart," and that "an abundant supply of oxygen is certainly highly important." The manner in which the deficiency of these blood constituents causes the inhibitory effects is suggested in the following lines of Langley's⁴⁰: "The decrease of rigidity in the inhibited muscular tissue shows that inhibition is not caused by the development of a contractile force acting in a direction opposed to the normal one and overpowering it. We are then brought to the conclusion that certain nerve impulses—the inhibitory nerve impulses—are able to *lessen* or to *stop* the chemical change *in the tissue* which leads to contraction."

The rôle of the "inhibitory" fibers (now generally considered as vagal, because they form part of the nerve bundles which have been known as the vagi, or pneumogastric nerves) thus corresponds with that of the sympathetic vasoconstrictors we have found, elsewhere, to restore the arterioles to their normal caliber after these vessels had been dilated by a motor or secreto-motor nerve to incite an exacerbation of functional

³³ Coats: Bericht d. k. Sachs. Gesellsch. d. Wissensch., S. 360, 1869.

³⁴ Gaskell: Philosoph. Trans., p. 1019, 1882.

³⁵ Stefani: Archives italiennes de biologie, T. xxiii, p. 172, 1895.

³⁶ Muskens: Pflüger's Archiv, Bd. lxxvi, Hft. 5 u. 6, S. 328, 1897.

³⁷ Gaskell: Schäfer's "T. B. of Physiol.," vol. ii, p. 169, 1900.

³⁸ Foster: "T. B. of Physiol.," sixth American edition, 1895.

³⁹ Porter: "Amer. T. B. of Physiol.," vol. i, second edition, p. 148, 1900.

⁴⁰ Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 616, 1900.

activity. Langley's observation gives precision to my view in this connection; interpreted from my standpoint, it is the diminution of blood in the cellular elements which serves "to lessen or to stop the chemical change in the tissue which leads to contraction." Can we logically, in view of the secreto-motor rôle ascribed by physiologists to the vagus in other organs, admit that in the heart its action is the opposite? That the so-called "inhibitory" nerve is composed of sympathetic fibers which carry on the same functions they do in other organs, is therefore evident.

Should we under these conditions consider the sympathetic as "inhibitory"? I have shown that inhibition is the result of excessive constriction of the arterioles. "Excessive" here obviously portrays a morbid or pathological condition, one of grave importance clinically. Indeed, as I will show in the second volume, many toxins and toxics are fatal owing to their vasoconstrictor influence on the cardiac vessels, and the morbid phenomena awakened are precisely those described above—those which the physiologist deems normal because they are expressions of a so-called physiological function he has termed "inhibition."

In my opinion the older term "moderator nerve" should replace the pernicious term now used, and "inhibition" be reserved for the expression of the morbid process which excessive constriction of the arterioles represents.

AUGMENTATION.—This action of the heart, *i.e.*, increase of its contractile power, must be due to an action other than that of accelerator nerves. Thus, von Bezold and Bever⁴¹ and later Cyon⁴² found that stimulation of the accelerator increased the number of beats of the heart, but not its power. This was confirmed by other investigators. Again the mode of action of the augmentor nerve differs strikingly from that of other cardiac nerves; Foster,⁴³ for instance, writes: "In contrast with the case of the vagus fibers, a somewhat strong stimulation is required to produce an effect; the time required for the maximum effect to be produced is also remarkably long." These

⁴¹ Bezold and Bever: *Untersuch. a. d. physiol. Lab. zu Würzburg*, Bd. II, 1887.

⁴² Cyon: *Loc. cit.*

⁴³ Foster: *Loc. cit.*, p. 203.

facts suggest that acceleration and augmentation are separate functions. Indeed, the delay in the augmentation of power, as compared with the acceleration, is explained when, as I urged a few years ago,⁴⁴ the adrenal secretion is regarded as the source of the increased cardiac power. This is sustained by many facts. Thus, while Noel Paton⁴⁵ refers to the "augmentors and accelerators" as small medullated, *i.e.*, sympathetic, fibers "which leave the spinal cord by the anterior roots of the second, third, and fourth dorsal nerves passing to the stellate ganglion," I have shown that the three above-mentioned roots are also precisely those through which the nerves which pass to the sympathetic chain and thence down to the splanchnic, to finally reach the adrenals. On stimulating these nerves, therefore, an experimenter not only excites the accelerators which pass to the heart via the annulus of Vieussens, but also the nerve-paths to the adrenals.

This accounts for the fact that while a large group of investigators including Cyon, Bezold, Schmiedeberg, Boehm and Bowditch observed acceleration without increase of power, others, equally competent, including Heidenhain, Mills, Roy and Adami, and Bayliss and Starling observed both phenomena. Indeed Schmiedeberg and Bowditch both urged the presence of two different sets of nerves to account for these specific effects, the one set influencing the cardiac beats, the other "acting upon the blood-pressure without influencing frequency." Now, the marked influence of the adrenal secretion upon the blood-pressure is well-known, and the delay in the appearance of "augmentation" is explained when it is borne in mind that the activity of secretory organs had to be awakened before the "augmentation", and the rise of blood-pressure could become manifest. Biedl,⁴⁶ in fact, found that stimulation of the divided splanchnic only caused an increased production of adrenal secretion after 7 to 9 seconds.

I submitted in the two preceding sections, the reasons which had led me to conclude that the adrenal secretion contributed to the contractile power of the right ventricle which

⁴⁴ Sajous: *Jour. Amer. Med. Assoc.*, Feb. 4, 1905.

⁴⁵ Noel Paton: "*Essential of Human Physiol.*," p. 243, 1905.

⁴⁶ Biedl: *Loc. cit.*

it reaches with the venous blood of the inferior vena cava. Now, Brown-Séquard⁴⁷ had many years earlier (1853) urged the predominating influence of the blood of this vein upon cardiac dynamism, a view sustained by Radcliffe (1855); but Castell having found that a frog's heart when detached failed to beat with increased vigor in carbonic acid gas, and overlooking the fact that some other substance in the venous blood might have acted on the heart, physiologists disregarded Brown-Séquard's observation. Additional evidence to this effect is submitted in the second volume.

The presence of "augmentor" and "pressor" fibers in the sympathetic splanchnic accounts for the fact long ago recorded by von Bezold and Bensen,⁴⁸ that section of both splanchnics lowered the blood-pressure as much as section of the spinal cord in the cervical region, while Strehl and Weiss found that, after removing one adrenal, the blood-pressure could be lowered by clamping the suprarenal vein of the remaining organ, thus depriving the blood of any adrenal secretion, and that by releasing this vein the blood-pressure was soon restored to its previous level. As I view the process, however, excitation of the lower segment of the upper sympathetic cord after dividing it should raise the blood-pressure. Bezold found that this procedure raised the blood-pressure as much as *seven times* its initial level; Ludwig and Thiry showed, moreover, that the same result could be obtained after severing all the nerves to the heart.

Augmentor effects attended by a rise of the blood-pressure may also be produced through the intermediary of another organ. Cyon and Aladoff⁴⁹ found that stimulation of the annulus of Vieussens (which also contains pure accelerator fibers) raised the blood-pressure. Cyon had already found in 1867 that when the cervical sympathetic was divided on a level with the inferior cervical ganglion, and its *upper segment* was excited the strength of the heart-beats was markedly increased.

⁴⁷ Brown-Séquard: *Exper. Researches applied to Phys. and Path.*, N. Y., London, and Paris, 1853.

⁴⁸ Von Bezold and Bensen: *Neue Würzberger Zeitung*, 1866: *Verh. d. Phys. med. Gesells.*, Würzburg, January, 1867.

⁴⁹ Cyon and Aladoff: *Bull. de l'Acad. des Sci. de St. Petersburg*, vol. vii, 1871.

A recent study of the question (1898)⁵⁰ by the same physiologist showed that these "reënforced pulsations" which he had at first ascribed to reflex action, were in reality due to the fact that the nerves which evoke these phenomena were distributed to the vessels of the thyroid gland and that it was the secretion of this organ which had produced the cardiac "augmentation." The manner in which the thyroid secretion could produce this effect is readily explained by the fact that, as I have shown, this secretion serves to sustain the functional efficiency of the adrenal center. Briefly, it is also through the adrenals—though indirectly—that Cyon produced "reënforced pulsations" of the heart.

The following conclusions seem to me, in the light of the foregoing facts, to summarize the functional mechanism of the heart:—

1. *The nervous supply of the heart is derived from the sympathetic system and is composed of two sets of nerves: the accelerator and the moderator (or inhibitory) nerves.*

2. *The accelerator nerves increase the rapidity of the contractions of the heart, by causing dilation of its arterioles and thus increasing the volume of blood admitted to its muscular elements.*

3. *The moderator (or inhibitory) nerves diminish the rapidity of the heart's contractions, by causing constriction of its arterioles and thus reducing the volume of blood admitted to its muscular elements.*

4. *"Augmentation," i.e., increased power of the heart's contractions is due to increased activity of the adrenals, whose secretion traverses the heart on its way to the lungs.*

As to the physico-chemical process involved—bearing in mind that the muscular elements are inherently contractile—they are, pending additional data, as follows:—

5. *The mechanical energy upon which the right heart depends is of two kinds: (1) the contractile action of the adrenal secretion brought to it by the inferior vena cava; (2) the continuous action of the oxidizing substance of the coronary arterial blood upon myosinogen formed from granules β , the latter being granulations derived from leucocytes.*

⁵⁰ Cyon: Arch. de physiol. norm. et path., vol. x, No. 5, p. 618, 1898.

6. *The adrenal secretion and the granulations β enter the right auricle and the right ventricle with the blood of the vena cava.*

7. *The adrenal secretion, owing to its direct action on muscular tissue, causes the walls of these cavities to contract alternately upon their venous contents and to force a small quantity of the latter into the Thebesian foramen and channels.*

8. *This blood then penetrates the interfibrillary spaces of Hente,—i.e., around the bare muscle-cells,—and its granules β are used by the latter to build up their myosinogen.*

9. *As the plasma of the coronary arteries and their terminals, the pericellular capillaries of the muscle-elements, contains oxidizing substance (adrenoxidase) contraction of the muscle-cells is induced as it is elsewhere in the organism.*

10. *The adrenal secretion and the granules β , which do not enter the Thebesian channels, are carried to the lungs with the venous blood of the right ventricle.*

11. *The mechanical energy of the left heart is supplied (1) by the oxidizing substance of the arterial blood, which penetrates its muscular structures and its cavities by the coronaries and the pulmonary veins, and (2) by an additional supply of granulations β , and perhaps of adrenal secretion, which find their way to its myocardium through the Thebesian channels that connect it with the right heart.*

12. *The manner in which the contractile process is carried on in the walls of the left heart is similar to that which prevails in the right heart.*

THE ADRENAL SECRETION IN ITS RELATIONS TO RESPIRATORY FUNCTIONS.

The rôle of the adrenal secretion in respiration, and particularly the process through which oxygen is taken up by the blood, was reviewed in the second chapter. I believe that the succeeding chapters, by affirming the importance of the oxidizing substance in every part of the organism, have but confirmed the conclusions reached concerning the process in question. The fact that the interchange of oxygen and carbonic acid between the alveolar air and the blood by mere diffusion was inadequate to account for the experimental results

of various investigators, particularly Bohr and Haldane and Smith, has therefore been correspondingly emphasized. I must also refer to the fact, however, that the belief of Ludwig, Bohr, and others, that the alveolar tissues might be the seat of functions capable of fulfilling the missing requirements of the process, has not been sustained by my inquiry. On the other hand, the rôle of the adrenal secretion in the lungs as I have defined it has adequately met these requirements, notwithstanding the severe tests to which it has been submitted in previous chapters.

We have seen that the adrenal secretion, conveyed to the lungs with the venous blood, is not only able to take up oxygen, but to form an oxidizing substance, *i.e.*, adrenoxidase, with which hamoglobin can, in the lungs, become replenished with oxygen. The entire set of analyses submitted in this work so far, however, has served further to emphasize another fact: *i.e.*, that *the plasma, and not the corpusele, is the dispenser of oxygen*, the corpusele being a mere carrier from which the plasma itself becomes replenished as needed. As already stated, this precisely coincides with the conclusion to which Jaquet was led by chemical methods after Salkowski (1881) had obtained oxidations from blood alone, which he attributed, however, to the blood-corpuseles. Abelous and Biarnés having obtained oxidation of salicylic aldehyde by means of blood-*serum*, Salkowski modified his former view and experimentally confirmed the results of the other investigators.

Finally, we have seen how closely connected the adrenal secretion is with the integrity of the blood, and how readily the hamoglobin molecule becomes dissociated in proportion as the efficiency of the adrenals becomes weakened.

The next important question to analyze is one fraught with considerable confusion, *viz.*, the manner in which the respiratory process is governed, and the identity of the respiratory center.

THE NERVO-VASCULAR MECHANISM OF THE LUNGS.

According to prevailing teachings the respiratory center is located in the medulla oblongata, *i.e.*, the bulb. But there is considerable evidence on record indicating that the bulbar

center is not supreme in the control of respiration, although the fact that it forms part of the controlling mechanism cannot be denied. Thus, division of the cord below the seventh cervical nerve arrests costal respiration; section below the medulla causes all thoracic movements to cease; removal of the brain *above* the medulla, the seat of the supposed center, does not stop respiration, while cessation of this function occurs when the medulla is removed or extensively injured, save in exceptional cases. After reviewing this evidence Professor Foster adds: "Nay, more; if only a small portion of the medulla—a tract whose limits have *not been clearly defined*,⁵¹ but which may be described as lying below the vasomotor center in the immediate neighborhood of the nuclei of the vagus nerves—be removed or injured, respiration ceases, and death at once ensues. Hence this portion of the nervous system was called by Flourens the vital knot, or ganglion of life: *nœud vital*. We shall speak of it as the *respiratory center*."

Yet, how account for the facts recited in the following quotation from Noel Paton's text⁵²: "Both parts of the respiratory center are under the control of higher nerve centers, and through these they may be thrown into action at any time, or even prevented from acting for the space of a minute or so. But, after the lapse of this period, the respiratory mechanism proceeds to act in spite of the most powerful attempts to prevent it.

"To determine its mode of action the influence of afferent nerves upon the center must be considered.

"*Vagus*.—Since the vagus is the nerve of the respiratory tract we should expect it to have an important influence on the center.

"*Section of one vagus* causes the respiration to become slower and deeper; but, after a time, the effect wears off, and the previous rate and depth of respiration is regained.

"*Section of both vagi* causes a very marked slowing and deepening of the respiration, which persists for some time, and passes off slowly and incompletely. Now, if after the vagi have been cut, the connection of the center with the *upper brain*

⁵¹ The italics are mine.

⁵² Noel Paton: *Loc. cit.*, p. 291.

tracts is severed, the mode of action of the center totally changes. Instead of discharging rhythmically it remains for a long period at rest, then the inspiratory center discharges violently, causing a strong and prolonged contraction of the muscles of inspiration. This passes off, and again a period of rest of variable duration sets in, to be again interrupted by another more or less long and strong discharge.

"Separation of the respiratory center from the vagi and upper brain tracts brings about a loss of its rhythmic action, *but does not stop its activity*. The center owes the rhythmic nature of its action to afferent impulses. These afferent impulses reach it normally through the vagi, but when these are cut the upper brain takes upon itself the function of maintaining the rhythm."

Howell⁵³ also says, referring to the "midbrain, at the level of the posterior colliculi" (the corpora quadrigemina) a region above the medulla oblongata: "Martin and Booker⁵⁴ found that stimulations in this region caused a marked increase in the rate of inspiratory movements and finally a standstill in inspiration—that is, a complete tetanic contraction of the inspiratory muscles lasting during the stimulation. Lewandowsky⁵⁵ has shown that section of the brain stem at or below the inferior colliculi causes an alteration in the respiratory rhythm similar to that following section of both vagi. After cutting through the inferior colliculi further sections more posteriorly do not add to the effect. He considers that there is an automatic inhibitory center in the midbrain which influences continually the automatic activity of the medullary center." Again, Ott⁵⁶ writes: "I have made numerous experiments to determine the exact seat of the polypnœic center. To establish a center three things are necessary: (1) that its abolition causes the phenomena to disappear; (2) that irritation—mechanical, chemical or electrical—causes the phenomena to be present, and (3) that the part of the nervous system exhibiting these peculiarities be circumscribed in extent. After numerous observations and

⁵³ Howell: "T. B. of Physiol.," second edition, p. 640, 1907.

⁵⁴ Martin and Booker: Jour. of Physiol., 1, 370, 1878.

⁵⁵ Lewandowsky: Archiv f. Physiol., 489, 1896.

⁵⁶ Ott: "T. B. of Physiol.," second edition, p. 451, 1907.

experiments it was found that pressure upon the tuber cinereum with a pledget of cotton, or even slight puncture, increased the normal respirations to the point of polypnœa. Complete puncture in a normal animal was followed by a rise to 106° F. within two hours, even though the animal was bound down and had been subjected to considerable shock.

"If now the animal whose tuber is punctured be heated, there will result *no* polypnœa, even though a temperature of 107° F. be reached. I am convinced that the *tuber cinereum is a center of polypnœa and thermotaxis.*"

A suggestive feature asserts itself in this connection: As I have pointed out, and as will be further shown in the second volume the tuber cinereum is precisely the region through which the nerve path from the pituitary body to the adrenals passes to the medulla oblongata, and thence, via the spinal cord and the sympathetic nerves and ganglia, to the adrenals, whose secretion, we have seen, serves to take up the oxygen of the air and to distribute it to the tissues, *i.e.*, to sustain oxygenation. Moreover, as emphasized by considerable evidence submitted in the second volume, the walls and floor (of which the tuber cinereum forms part) of the third ventricle, are the pathways of a vast array of sympathetic fibers which likewise pass from the posterior or neural lobe of the pituitary (via the nucleus magnus grisei) to the medulla and cord and thence to be distributed through the sympathetic chain and its offshoots to all parts of the body including the lungs. We have here the explanation of the presence of so-called heat and respiratory centers in this region, *i.e.*, irritation phenomena following the experimental lesions in the course of these nerve-paths,—a fact further sustained by the observation of many experimenters that removal of the pituitary body—the seat of the heat and main respiratory centers in the light of my views—is followed by marked lowering of the temperature and dyspnœa.

How does the respiratory center—or centers, for as stated, the bulbar center is endowed with important functions—influence the respiratory mechanism? Before this feature of the subject can be analyzed, a brief review of the circulation and innervation of the lungs may prove advantageous.

The pulmonary circulation as regards vascular distribu-

tion is succinctly portrayed in the following description by Miller,⁵⁷ as given by Böhm and von Davidoff⁵⁸: "The *pulmonary artery* follows closely the bronchi through their entire length. An arterial branch enters each lobule of the lung at its apex, in close proximity to the bronchus. After entering the lobule the artery divides quite abruptly, a branch going to each infundibulum; from these branches the small *arterioles* arise which supply the alveoli of the lung. 'On reaching the air-sac the artery breaks up into small radicles, which pass to the central side of the sac in the sulci *between* the air-cells, and are finally lost in the rich system of capillaries to which they give rise. This net-work surrounds the whole air-sac and communicates freely with that of the surrounding sacs.' This capillary net-work is exceedingly fine, and is shrunken *into* the epithelium of the air-sacs; so that between the epithelium and the capillary there is only the *extremely delicate* basement membrane. The infundibula, the alveolar ducts and their alveoli, and the alveoli of the respiratory bronchioles are supplied with similar *capillary net-works*. The veins collecting the blood from the lobules lie at the periphery of the lobules in the interlobular connective tissue, and are as far distant from the intralobular arteries as possible. These veins unite to form the larger pulmonary veins. The bronchi, both large and small, as well as the bronchioles, derive their blood-supply from the *bronchial arteries*, which also partly supply the lung itself. Capillaries derived from these arteries surround the bronchial system, their caliber varying according to the structure they supply: finer and more closely arranged in the mucous membrane, and coarser in the connective-tissue walls. In the neighborhood of the terminal bronchial tubes the capillary nets anastomose freely with those of the *respiratory* capillary system." To avoid confusion I may recall the fact that, while the *pulmonary* artery and its branches contain *venous* blood, and the *bronchial arteries* and their branches carry *arterial* blood, the *pulmonary veins*, on the contrary, contain *arterial* blood. When, therefore, bronchial capillaries are said to empty

⁵⁷ Miller: *Journal of Morphology*, vol. viii, p. 165, 1893.

⁵⁸ Böhm and von Davidoff: *Loc. cit.*

into the pulmonary veins, it is not used, or venous, blood that is transferred to the latter, but arterial blood originally derived from the thoracic aorta or its primary branches.

The lungs, as is well known, are innervated by the vagus and the sympathetic system. These unite to form plexuses, the anterior and posterior, which enter the organs with the bronchial tubes and accompany them along their ramifications. The anterior pulmonary plexus, made up of vagal and sympathetic filaments, overlies the pulmonary artery, while the richer posterior pulmonary plexus, composed also of vagal filaments, intermixed with sympathetic fibers from the second, third, and fourth thoracic ganglia, follows the bronchi to their ultimate subdivisions.

According to prevailing views, the vagus—both its sensory and motor fibers—is alone regarded as the intermediary between the respiratory center and the organs of respiration, but as shown in the second volume, the neural lobe of the pituitary also contains the sympathetic center. This proximity to the respiratory center and the important rôle the sympathetic plays in respiration pointedly suggest that both centers are functionally united.

Indeed, there is good ground for the belief that the experimental phenomena now ascribed to the vagus are partly of sympathetic origin—sympathetic in the sense that they are essentially vasoconstrictor as in other organs previously reviewed. Sappey, for instance, writes⁵⁹: “Section of both pneumogastrics in the median portion of the neck not only abolishes the sensibility of the respiratory mucous membrane and paralyzes the internal respiratory muscles; it also involves as consequence a mucous *effusion* into the bronchi, *engorgement* of the lungs, emphysema of these organs, and a very sensible diminution in the number of inspirations.” We have in the pulmonary engorgement an evident result of variation of vascular caliber, and inasmuch as we are dealing with a *division* of the nerve, the effect on the vessel must have been one of relaxation. On the other hand, we have in the paralysis of the internal respiratory muscles evidence that a motor nerve—

⁵⁹ Sappey: “*Traité d'Anatomie Descriptive*,” vol. III, p. 397.

a vasodilator, or stricto-dilator, in our sense—was also severed. These dual phenomena indicate that the vagus, as we have seen in the case of the heart, must have contained vasoconstrictor, *i.e.*, sympathetic fibers.

The presence of vasoconstrictor fibers is, in fact, generally recognized. François-Franck, in 1881, showed that the sympathetic nerves distributed to the lungs, caused vasoconstriction, these fibers being stimulated at the entrance into the lungs. Bradford and Dean⁶⁰ also demonstrated the presence of vasomotor nerves in these organs after a series of exhaustive experiments. In a subsequent study of the subject François-Franck⁶¹ noted the paradoxical fact that vasoconstriction of the pulmonary vessels caused the lungs to swell, instead of being reduced in volume. This is readily accounted for when it is recalled that the vasoconstriction applies only, in the light of my views, to the arterioles. These small pre-capillary vessels being constricted, the arterial blood was dammed up behind the seat of obstruction in François-Franck's experiment, thus causing the larger portions of the vessel, which are not governed by the sympathetic, to dilate.

A source of confusion asserts itself in this connection, however, which we have also encountered while studying the heart. The experiments of Rose Bradford and Dean⁶² are thus referred to by François-Franck: "They carefully sought the points of emergence, from the cord, of the filaments which cause elevation of pulmonary pressure and lowering of aortic pressure: that is to say, pulmonary vasoconstriction. These were located from the second to sixth dorsal, and, in respect to maximum effects, on a level with the third, fourth, and fifth nerves. The pulmonary vasoconstrictors ascend the chain up to the first thoracic ganglion, where they become detached, to reach the pulmonary plexuses." The salient feature of the topography of these nerves is that the lower limit of the ganglionic chain through which they pass happens to be the upper limit of the ganglia from which the splanchnic nerves that ultimately carry impulses to the adrenals are given off. While the pulmonary

⁶⁰ Bradford and Dean: *Jour. of Physiol.*, vol. xvi, p. 34, 1894.

⁶¹ François-Franck: *Arch. de Physiol.*, T. viii, p. 184, 1896.

⁶² Rose, Bradford and Dean: *Journal of Physiol.*, p. 57, 1894.

vasoconstrictors which pass directly to the lungs from the first thoracic to the pulmonary plexuses are, as generally taught, true vasoconstrictors, the presence in the second, third, and fourth ganglia of the sympathetic chain, of the nerves to the adrenals suggests that many vasoconstrictor phenomena attributed to the direct action of nerves, should be ascribed to an increase of adrenal secretion in the blood. Indeed Jacobi⁶³ found that intense vasoconstriction of the intestinal vessels (inhibition) produced by excitation of the splanchnic was replaced by ordinary vasoconstriction after the suprarenal nerves had been cut.

The fact, moreover, that the introduction of adrenal extract into the circulation produces general vasoconstriction is well known. Mankowsky,⁶⁴ for example, noted "a great increase in blood-pressure and stimulation of the cardiac and respiratory centers." This occurred "even when the animals (dogs) were under the influence of chloroform, morphine, or chloral hydrate." "In cats, says Swale Vincent,⁶⁵ "by far the most noticeable feature was an enormous rapidity of the respiratory movements in the early stage." The two—now familiar—stages that occur under the influence of toxic doses of suprarenal extract, as well as under that of other poisons, are well illustrated in the following observation by the same investigator: "In the early stage of poisoning respiration is quick and shallow and the heart is excited. Subsequently the breathing and heartbeats become feeble, and finally the respiration is deep and infrequent." Finally, the fact that all these phenomena are independent of the cord has been shown by Biedl,⁶⁶ who, as we have seen, obtained marked increase of blood-pressure after injections of suprarenal extract, notwithstanding the fact that all the spinal structures had been removed.

This does not mean that the adrenal secretion fulfills any particular function in the lungs other than that of taking up oxygen therein; it is only intended to show that excitation of the splanchnic nerve may suggest the presence of pulmonary

⁶³ Jacobi: *Archiv f. exper. Path. u. Pharm.*, vol. xxix, p. 171, 1892.

⁶⁴ Mankowsky: *Russian Archives of Pathology*, etc., Mar, 1898.

⁶⁵ Swale Vincent: *Jour. of Physiol.*, Feb. 17, 1898.

⁶⁶ Biedl: *Wiener klin. Wochen.*, ix, 1896.

vasoconstrictor nerves in this great nerve-path, when the vasoconstrictor effects witnessed in the lungs are in reality due to the presence in the blood, as a result of splanchnic stimulation, of an excess of adrenal secretion.

As to the rôle of the vagus in the respiratory organs, our views differ from those at present taught only in that they explain, as was the case with other organs, *how* the physiological phenomena are produced.

I have briefly referred to the manner in which the vagal fibers are distributed in the lungs. Sappey⁶⁷ also studied the distribution of vagal nerves in the lungs of mammals, including particularly those of man, the ox, and horse, and reached the following conclusions: "1. They follow the subdivisions of the air-tree to their terminal extremities; they do not leave these subdivisions and follow them to the lobules. 2. All those that leave the anterior pulmonary plexus and the much greater number given off by the posterior pulmonary plexus preserve their plexiform arrangement throughout their entire distribution; their meshes are elongated only in the line of their axis, each thus constituting an elongated ellipse. 3. Their ramifications, essentially destined for the muscular coat of the bronchi and respiratory mucous membrane, have no connection with the blood-vessels." Berdal, on the other hand, confirms this, and indicates the rôle of the sympathetic terminals in the following lines: "The branches of the pneumogastric are destined for the bronchi; the branches of the great sympathetic are lost in the walls of the arteries."

The statement of Sappey that the vagal ramifications of the vagus have no connection with the blood-vessels, introduces a feature of importance which applies to all other organs reviewed, viz.: that besides the vasodilator and vasoconstrictor nerves which govern the function of any organ, there are sensory terminals which, as such, transmit afferent impulses to the centers (primary or subsidiary) which govern the local blood supply. Indeed, we have seen that section of the vagi in the neck caused loss of sensation in the respiratory mucous membrane, paralyzed the bronchial muscles, and gave rise to effusion of

⁶⁷ Sappey: *Loc. cit.*, p. 391.

mucus into the bronchi and engorgement of the lungs. How can all these phenomena be accounted for without granting sensory as well as motor and vasomotor functions to the vagal supply? Loss of sensation points to inhibited function, and not to engorgement of the bronchial mucous membrane. And yet we may have engorgement without functional erethism, if it is due, not to the presence of blood fully charged with oxygen, but to blood which, through the very fact of being dammed up in the vascular channels, is reduced therein to practically the condition of venous blood. The effusion of mucus into the bronchi and pulmonary engorgement would occur as normal consequences of such a state of things. But how account for this vascular dilation without granting such attributes to the vagal plexuses?

Again, the fact that cutting of both nerves in the neck gave rise to paralysis of these muscles points to another suggestive feature, namely: that the vagus must *incite* and *govern* the motor impulses to these muscles, besides presiding over the functional variations of caliber of their vessels. If we now add to these manifestations of *efferent* nervous activity those of *afferent* activity suggested by the loss of sensation over the bronchial mucous membrane, it seems clear that *we have in the vagal nerves referred to an autonomous supply especially devoted to the function of the bronchial tubes and their ramifications down to—but not including—the pulmonary lobule.* The importance of this fact asserts itself when we realize that it accounts for the complete isolation of bronchial affections from those of the parenchyma, and gives us a clue to their original cause.

My opinion that the vagus—as motor nerve—acts in the lungs as elsewhere, *i.e.*, as stricto-dilator nerve, is sustained by experimental evidence. As Noel Paton writes⁹⁸: “Strong stimulation of the pulmonary branches of one vagus (below the origin of the superior laryngeal) causes the respiration to become more and more rapid, the inspiratory phase being chiefly accentuated. If the stimulus is very strong respirations are

⁹⁸ Noel Paton: *Loc. cit.*, p. 292.

stopped in the phase of inspiration. Weak stimuli, on the other hand, may cause inhibition of inspiration.

"Such experiments prove that impulses are constantly traveling from the lungs to the center whereby the rhythmic activity of the center is maintained.

"How do these impulses originate in the lungs? Apparently from their alternate expansion and contraction.

"If the lungs be forcibly inflated—*e.g.*, with a bellows—the inspiration becomes feebler and feebler and finally stops. The nature of the gas, if non-irritant, with which this inflation is carried out is of no consequence. If, on the other hand, the lungs be collapsed by sucking air out of them, the inspiration becomes more and more powerful, and may end in a spasm of the inspiratory muscles.

"This shows that with each expiration a stimulus passes up the vagus which acts upon the inspiratory center to make it discharge. The vagus is thus a *true excito-motor nerve*, making the center act in a reflex manner. With each collapse of the lung the vagus is thrown into action, as the lungs expand it ceases to act, and, as a result, the inspiratory center stops acting, the muscles of inspiration cease to contract, and expiration occurs.

"While ordinary respiration may thus be considered as a rhythmic reflex act, it must not be forgotten that the respiratory center can and does act rhythmically under the influence of the higher center, or a-rhythmically and spasmodically when these as well as the vagi are severed from it."

The mode of action of the vagus as a "true excito-motor nerve" is thus subject in a great measure to the respiratory centers—the main one of which, in the light of my views is located in the neural lobe of the pituitary body. The vagal sensory terminals of the bronchi transmit sensory impulses to this center and excito-motor impulses are transmitted by it to the entire respiratory apparatus, including the thoracic respiratory muscles. The manner in which all these muscles are excited to increased activity by the efferent or excito-motor vagal fibers does not differ from that of all organs reviewed: an excess of blood is admitted into the contractile elements, through dilation of its arterioles. An excess of blood-plasma laden with

oxidizing substance is admitted, as previously shown, to the myosinogen of the muscular elements, where inspiration is in order; hence the fact that strong excitation of the vagus "causes the respiration to become," as Paton says, "more and more rapid, the inspiratory phase being chiefly accentuated." When—physiologically—excessive inspiration is to cease, the sympathetic vasoconstrictors come into play: they restore the muscular arterioles to their normal caliber; less blood is admitted to the muscular elements and the inspirations resume their normal rhythm.

But a third factor must now be taken into account: that represented by the functions of the adrenals. And from the standpoint of the clinician, this factor is by far the most important of all the physiological phenomena of the function of respiration. Indeed as will be shown in the second volume, dyspnœa is often the result of adrenal insufficiency, the adrenal secretion produced being inadequate to sustain the oxygenation of the body at large. Again, Miller, we have seen, refers to the subdivision of the pulmonary artery "which divides quite abruptly, a branch going to each infundibulum"; from the latter "small *arterioles* arise which supply the alveoli," while these on reaching the air-sac are said to culminate in "the rich system of capillaries to which they give rise." If the "small arterioles which supply the alveoli" are abnormally dilated through some general dyscrasia and the stream of venous blood of oxygenation of the adrenal secretion it contains is thus imperfectly exposed to the air, we have a logical explanation of the well known beneficial action of belladonna—a sympathetic stimulant which, as we will see, causes constriction of the arterioles, and of potassium iodide, a powerful adrenal stimulant.

That fluctuations in the secretory activity of the adrenals may provoke dyspnœa is well illustrated by the effects of all drugs that are sufficiently active to markedly affect adrenal functions. The action of venoms even more strikingly shows the morbid connection that exists between variations of suprarenal activity and pulmonary functions, even the stage of blood-disintegration being sometimes reached. Noé,⁹⁹ for instance,

⁹⁹ Noé: *Loc. cit.*

refers to the many observers who have reported intense respiratory phenomena after cobra-bites. Viper-venom was also found by Phisalix to produce at first "accelerated respiration," then "somnolence, with slowing of respiration." Bee-venom in sufficient quantity gives rise to dyspnoea, according to Paul Bert, *black blood* being found in the vessels. Toad-, salamander-, scorpion-, and eel-venoms were found to affect respiration in a similar manner. Mosso noted that the process of death varied with the dose: medium doses first arrest respiration, then the heart; stronger doses arrest both simultaneously. Paralysis of the motor end-plates had evidently nothing to do with this process, since Mosso found the thoracic nerves responsive to the induced current.

Removal of the adrenals under these conditions should give rise to phenomena similar to a violent dose of venom. Cybulski not only observed,⁷⁰ under such conditions, marked dyspnoea, a fall of the vascular pressure to zero, and hæmoglobinuria, but also found that the injection into the veins of an aqueous 10-per-cent. solution of suprarenal extract "immediately caused these phenomena to disappear." Boinet⁷¹ states that after removal of both organs in a large number of rats the respiration became "slow, painful, and difficult." Briefly, the functions of the adrenals are as important features of the respiratory function as any of those generally recognized. It is now possible to understand why the nerve paths of the heat and respiratory centers are so intimately related in the third ventricle. Originating from a common center, the pituitary body, the vagal, sympathetic and adrenal nerves, jointly project from their common source, the pituitary body, to reach, by way of the tuber cinereum, the walls of the third ventricle and the midbrain, the medulla oblongata, where they form subsidiary (and probably coördinating) centers whence the impulses to the respiratory organs are transmitted.

The newer features of the nervo-vascular mechanism of (ordinary tranquil) respiration which I submit in the foregoing pages, pending additional evidence and detail, may be summarized as follows:—

⁷⁰ Cybulski: *Gazeta Lekarska*, March 23, 1895.

⁷¹ Boinet: *Loc. cit.*

1. *The bulbar respiratory center is not, as now believed, the sole, or even the most important, center of this class; it is a subsidiary and, probably, a co-ordinating center.*

2. *The primary and chief respiratory center is located in the pituitary body and consists of three functionally related centers, the adrenal, vagal, and sympathetic centers, which, in turn, are connected by nerve-chains with the corresponding subsidiary centers in the bulb, and govern, through the intermediary of the latter, the respiratory mechanism.*

The chief respiratory center carries on its functions as follows:—

Its adrenal center, by governing the production of the adrenal secretion, which takes up the oxygen of the air and forms the albuminous constituent (96 per cent.) of haemoglobin, regulates the proportion of this oxidizing substance (the adrenoxidase) supplied to the blood.

Its vagal center, acting through the vagus (the intercostals and phrenic) as excito-motor (stricto-dilator) nerves of inspiration, provokes contraction of the muscles which dilate the larynx, the bronchi, and the thorax and depress the diaphragm, and thus increase the intake of air by the lungs, i.e., the supply of oxygen from which the adrenal secretion and the haemoglobin absorb oxygen to distribute it to the tissues.

Its sympathetic center, acting, through the sympathetic nervous system, as antagonist of the vagal center to provoke expiration, causes all the above-mentioned respiratory muscles to relax passively (by constricting their arterioles), thus enabling the larynx and bronchi to resume their normal caliber, the thorax to contract, and the diaphragm to rise, in order to insure the expulsion of the expiratory air laden with carbonic acid.

THE ADRENAL SYSTEM AND THE FUNCTIONS OF THE THYMUS GLAND.

In the first edition of this work (1903) I urged that there was "considerable analogy between the effects of thymus on the organism and those of the thyroid." Parhon and Golstein⁷² have since been led also to conclude that "the relations of the

⁷² Parhon and Golstein: *Secretions Internes*, p. 590, 1909.

thymus with the thyroid gland seemed very close," a view also sustained by the recent experiments of Hoskins.⁷³ Ruhräh⁷⁴ has, in fact, reported eighteen cases of infantile marasmus in which the thymus alone showed lesions—a fact which suggests that, as is the case with the thyroparathyroid apparatus, the thymus influences in some way general metabolism. In keeping with this view is the conclusion of Basch⁷⁵ that a relation exists between the thymus and the growth of bones and also the healing of fractures—also a therapeutic property shown by thyroid preparations. Conversely, Fischel⁷⁶ and others have observed no clearly defined evidence that removal of the thymus influenced development, general or osseous, of young animals.

Still, the preponderating evidence sustains the positive view, negative evidence being often due to faulty technique, or ascribable to the assumption of functions by the related organ—the thyroid in the present instance.

Svehla⁷⁷ believes that the thyroid gland only assumes its functions at birth, extract of foetal thyroid having proven inert, while extract obtained from the thyroids of infants during the first month of life was effective. Precisely in the same manner did thymus extract behave: foetal-thymus extract produced no effect, while that obtained from the thymus glands of infants in the first month caused increase in the frequency of the pulse and lessened blood-pressure. He found, moreover, that "among children of the same age the thymus extract is the strongest; less so the thyroid, and still less the adrenal. In adults, however, the adrenal outstrips both other glands."

Svehla refers to "increased frequency of the pulse and lessened blood-pressure" as the prominent effects of thymus extract: evidence, if its action corresponds to that of thyroid, that a toxic dose had been administered to the experimental animal. This is sustained by the fact that other typical symptoms were present: *i.e.*, muscular weakness, dyspnoea, and general collapse,—a condition from which the animals could be saved by the timely administration of thymus extract, which promptly restored the normal vascular pressure.

⁷³ Hoskins: *American Journal of the Medical Sciences*, Mar., 1911.

⁷⁴ Ruhräh: *British Medical Journal*, Aug. 29, 1903.

⁷⁵ Basch: *Jahrb. f. Kinderheilk.*, p. 1063.

⁷⁶ Fischel: *Zeitsch. f. exper. Pathol. u. Therap.* B. 1, p. 338, 1905.

⁷⁷ Svehla: *Archiv für exper. Pathologie*, Bd. xliii.

Thymus extract seems to prove efficacious in precisely the same class of cases of exophthalmic goiter—but *only when the asthenic or second stage is reached*—as thyroid extract. Owen,⁷⁸ for example, recalled his successful result in a marked case of twenty years' standing, but he indirectly points to his patient's advanced condition by the statement "the next three months he spent mostly in bed." His second case complained of feeling "low and weak," sweated profusely, became bald, and had tremors and pigmentation. A third case benefited was one in which breathlessness, general weakness, and emotional outbreaks prevailed. He also refers to an extremely aggravated case treated successfully by Maude,⁷⁹ in which drugs, including belladonna, had proven ineffectual. Under thymus tabloids, 45 grains daily, the patient rapidly improved, and invariably relapsed when they were discontinued. Maude having observed that the tremors were particularly relieved by this form of treatment, Owen tried fresh thymus in paralysis agitans, "with the result that the tremors were unmistakably benefited and the mental state and the muscular condition greatly improved."

An analytical study of Maude's cases shows that they are all of the advanced type. In the first "the heart and paralytic conditions were such as to confine her to bed for over a year." The second "belonged to a highly neurotic family; goiter had existed since childhood," and the "tremor, excessive muscular weakness, and cardiac disturbance were all well marked." The third had recovered from a previous attack without thymus; hence, its use after recurrence as the result of grief cannot serve as fair example. The fourth was of thirty-two years' standing, and the patient had suffered from "various severe nervous symptoms, viz.: paralysis of various basal nerves ophthalmoplegia, paralysis of facial, ambulatory epilepsy, etc." . . . "She had had, in 1894, twenty-four motions in one day of almost pure arterial blood. In November, 1895, she had a sudden profuse hæmatemesis, followed by collapse so extreme that she seemed moribund. After she rallied she was given 45 grains of thymus tabloids per day, for a month, and

⁷⁸ Owen: *British Medical Journal*, Oct. 10, 1896.

⁷⁹ Maude: *Lancet*, July 18, 1896.

her improvement was very remarkable; she remained in a fair state of health for many *months*." Degeneration of the arterial walls probably existed in this case, and it seems likely that the loss of blood can be credited with the relief afforded. Todd's case⁸⁰ had an epileptic mother, her sister had suffered from *myxædema* and had been cured with thyroid extract, and she was herself a "very delicate" girl. N. J. McKie's case⁸¹ and those of R. T. Edes⁸² and Philip James⁸³ also represent instances in which there was thyro-adrenal insufficiency. In a case successfully treated by Boisvert⁸⁴ the presence of melancholia also shows that weakened adrenals were present and that the increased insufficiency of these organs brought on by the thymus, as was the case with two of the patients referred to by Dr. Winter in which thyroid extract was used, led to recovery. These examples, which could be multiplied, not only indicate that thymus extractives are active when there is impaired functional activity of the thyroid and adrenals, but they also tend to prove that the thymus gland is very similar to the thyroid in its action upon these organs.

The harmful effects of thymus in the first stage are illustrated by a case described by Watson Williams,⁸⁵ who found that it aggravated the tachycardia and pyrexia: evidence that it had been given while thyroid overactivity was present. In the large proportion of cases reported, however, there is no marked untoward effect produced. It seems to be much less active in this connection than the thyroid extractives. In fact, in some cases—probably those on the border-line of thyroid insufficiency—it appears to act as a nutrient tonic, as noted by Hector Mackenzie⁸⁶ after a study of twenty cases in which he had tried thymus gland, and to which further reference is made below.

The connection between the thymus and the adrenals may also be illustrated by the experiments of Abelous and Billard,⁸⁷ in which removal of the former gave rise to symptoms similar

⁸⁰ Todd: *British Medical Journal*, July 25, 1896.

⁸¹ N. J. McKie: *British Medical Journal*, March 14, 1896.

⁸² R. T. Edes: *Boston Med. and Surg. Journal*, Jan. 23, 1896.

⁸³ Philip James: *Australasian Med. Gazette*, July 20, 1897.

⁸⁴ Boisvert: *Revue Médicale de Montréal*, June 21, 1899.

⁸⁵ Watson Williams: *Clinical Journal*, Dec. 11, 1895.

⁸⁶ Hector Mackenzie: *American Journal of the Medical Sciences*, April, 1897.

⁸⁷ Abelous and Billard: *Archives de Physiologie*, Oct., 1896.

to those that follow adrenalectomy: even to discoloration of the skin, great muscular weakness—lapsing into paralysis, blood-changes, œdema, etc. They also found that the secretions of the experimental animals were markedly toxic: evidence of inadequate oxidation. On the whole, this evidence, considered collectively, seems to indicate that *the thymus gland supplies some substance which directly or indirectly stimulates the secretory functions of the adrenal system, and thereby enhances the activity of the oxidation processes.*

What is the nature of the agency through which the thymus stimulates the adrenals, and what is the specific relationship between these organs? These questions are suggested by the fact that, while undue activity of the thymus increases that of the adrenals, there seems to be no evidence that the thymus can alone—i.e., independently of the thyroid—give rise to either exophthalmic goiter or myxœdema. In all cases of the former disease ascribed to the thymus found in available literature there is invariably thyroidal involvement. Yet the thymus seems sufficiently active to bring the adrenals to their normal activity when the general vital processes are depressed. We have seen, on the other hand, that its removal gives rise to symptoms recalling those of adrenalectomy.

Baumann⁸⁸ found minute quantities of iodine in the thymus also; but other experimenters have failed to find even this trace, and have ascribed Baumann's findings to contamination from neighboring thyroidal tissues. Even granting that such a trace of iodine exists, we are well aware that the thyroid does not owe its power to stimulate the adrenals to "a trace"; the labors of many investigators have conclusively shown that it must supply the organism with a considerable amount of this substance. Evidently we must look elsewhere for the solution of this problem, and, data bearing directly upon the subject being wanting, we shall have to seek for the required substance through its comparative behavior in the organism, and the manner in which its effects vary in the latter from those of thyroid extractives.

Valuable in this connection are the autopsies of 61 children at the Hôpital des Enfants-Malades, of Paris, performed

⁸⁸ Baumann: *Münchener med. Wochenschrift*, p. 311, 1896.

by Albert Katz at the request of Bourneville.⁸⁹ All these children had died of various diseases, their ages varying from one month to thirteen years, though 41 were under two years of age. In *all* of the 61 bodies the thymus gland was *present*, while in 28 mentally weak and epileptic children examined by Bourneville the thymus was *absent in 25*. In another series, of 292 cases, it was absent in 74 per cent. But these comprise not only all varieties of mentally abnormal children, but also various degrees of imbecility; so that the remaining 26 per cent. may have included a number of instances in which mental development was high as compared to that of the cases in which the organ was absent. Yet, to avoid favoring our own line of argument, we will consider that in three-fourths of imbecile children, some of which were epileptics, the thymus gland was absent.

These observations become elucidative when analyzed through the effects of thyroid extract. Especially suggestive is the following casual remark of Cabot's, in the course of a valuable paper published some years ago⁹⁰: "The fact that in myxœdematous children and cretins the thyroid treatment is associated with notable growth in height has led some observers to try its effects in dwarfed children not myxœdematous, to see if their development could not be helped. I have collected 10 such cases, 3 in idiotic children and 6 in whom the lack of development was mainly physical. A considerable increase in height was observed in all the cases, *but the mental symptoms were not improved.*"⁹¹ It seems evident that if, on the one hand, the vast majority of cases of mentally weak children do not possess thymus glands, and that, on the other, thyroid extract will enhance growth of idiotic children (not myxœdematous ones, *i.e.*, cretins), the oxidation processes, stimulated by the thyroid simultaneously with the adrenals, are inadequate to alone bring on improvement of the mental symptoms. Again, it becomes evident that it is upon the thymus that the mental development depends, and, finally, that it is to some agent which the thyroid gland does not contain that this development is due.

⁸⁹ Katz: *Le Progrès Médical*, June 23, 1900.

⁹⁰ Cabot: *Medical News*, Sept. 12, 1896.

⁹¹ The italics are my own.

This enables us to eliminate iodine, *i.e.*, thyriodase, as the main active principle of the thymus gland, and, our inquiry being disconnected from the oxidation process through the evident inefficiency of the thyroid to restore mental functions, we are led to seek for a chemical body that will enhance cerebral nutrition. Can we expect such an hypothetical agency, however, to concentrate its effects upon the brain alone? This is hardly probable, judging from analogy, and the nervous system at large must also utilize it physiologically. Our field is therefore broadened, since an agency connected with the nutrition of the brain alone, or one playing the same rôle in respect to the entire nervous system, may serve our needs. This is, to say the least, fortunate, for the chemistry of brain- and nerve- matter is far from well known, and even a good analysis—*i.e.*, one based upon the more salient data available—would be impossible were the limits of the inquiry at all narrowed.

Of the solid constituents of nerve- and brain- matter, three stand out prominently: cholesterin, cerebrin, and lecithin. Cholesterin, considered by Austin Flint, Jr., as a waste-product of cerebral and nervous origin, though it represents one-half of all the solids, shows no molecular constituent capable of assisting us ($C_{26}H_{44}O$), the fact that the thyroid secretes a specific agency being taken as standard; nor does cerebrin ($C_{17}H_{33}NO_3$), though both this and the preceding body are found in abundance in the cerebro-spinal axis and nerves. With lecithin, sometimes termed "phosphorized fat," which represents about one-tenth of the solids, the case is different, since its formula ($C_{44}H_{90}NPO_6$) suggests that phosphorus may represent the constituent we are seeking. It is not only a prominent component of the whole cerebro-spinal and nervous systems, however, but it is also a constituent of the red and white corpuscles, milk, bile, serum, semen, and pus. Another body, protagon ($C_{100}H_{308}N_5PO_{35}$), has also been isolated from brain-substance by Liebreich, who considered it as the main cerebral constituent: an opinion sustained by Gamgee and Blankenhorn.⁹² Hoppe-Seyler and other investigators are, however, inclined to consider it as a mixture of lecithin and cerebrin. Whether this be the case or not, phosphorus again

⁹² Gamgee and Blankenhorn: *Journal of Physiology*, vol. II, 1879.

appears as the only element capable of being at all associated with the question in point.

To adopt organic phosphorus as the characteristic constituent of the thymus gland, however, and declare that it is through its *minus* or *plus* production that the mental attributes of children are developed, would merely constitute a theory. As a stronger position is desired for all the deductions vouchsafed in this work, collateral evidence must be sought.

The observations of Cabot, that, while thyroid extract stimulates growth, it fails to enhance mental development in idiots other than myxœdematous ones, raises the question as to whether such results can be due to the absence of phosphorus in the thyroid. If such is the case, the absence of this element should also show itself in the results obtained from the extract in some other disease, if any structure other than the brain and nervous system, in which a morbid deficiency of phosphorus also exists, is a feature of that disease. We know, for example, that phosphorus is introduced into the organism with food, and that calcium phosphate, by becoming deposited in the bones, gives them their hardness. Is there any evidence that the bones of subjects in which thyroid extract is successfully administered lack of this hardening constituent? Referring to the use of thyroid extract in cretinism, T. Telford-Smith²³ makes the following statement: "I have found that during thyroid treatment the rapid growth of the skeleton leads to a softened condition of the bones, resulting in a yielding and bending of those which have to bear weight, and, as cretins under treatment become more active and inclined to run about, this tendency to bending has to be guarded against." After referring to the experiments of Hofmeister in rabbits and those of Eisenburg in sheep and goats in which bending of the legs was caused by removal of the thyroid, he adds: "While in rickets, however produced, there is perverted and delayed ossification resulting in softening and bending of the bones, under thyroid treatment in cretinism there is rapid resumption of growth in the skeleton, leading to softening, which is most marked in the long bones and at the epiphyses." That we are dealing here with an absence of phosphorus and

²³ T. Telford-Smith: *Lancet*, Oct. 2, 1897.

that the calcium phosphate serves to harden the bones concurrently with their growth seem obvious.

But why does this not occur in all cases? Simply through the fact, ascertained by Marie,⁹⁴ that the thymus is almost always persistent in cases of cretinism. When thyroid gland is administered, therefore, the increased oxidation procured with the aid of the adrenals also enhances thymic activity, and the assimilation of phosphorus is increased in proportion. This is proven by the experiments in animals by Hofmeister and Eisenburg, referred to by Telford-Smith. If removal of the thyroid caused bone-softening in these, it is because—in the light of my conception of the process—the adrenals were rendered inadequate, and, oxidation being impaired in proportion, the thymus also failed functionally.

This process, however, involves the need, in the structures of the thymus gland, of a metabolic process culminating in the production of an internal secretion laden with phosphorus-containing bodies. Quotations from a study of the *nucleins and nucleoproteids* in their relation to internal secretion by Chittenden⁹⁵ will serve to enlighten us: "The manufacture of the specific substances which give character to the various internal secretions is obviously a function either of special cells contained in the gland or it may be in some cases an inherent quality of all the cellular elements of a given gland. In the pancreas the formation of the active agent is apparently limited to an interstitial, epithelium-like tissue occurring in isolated patches throughout the gland and especially characterized by its vascularity. This epithelioid tissue is certainly distinct from the secreting alveoli, and is suspected, at least, of being the source of the internal secretion. Again, in the adrenals, as Schäfer and Oliver have shown, the active principle, which has such a marked influence upon the heart and arteries, is contained only in the medulla of the gland, and not in the cortex, the medulla forming about one-fourth of the gland by weight." . . . "If we take the content of phosphorus as a measure of the proportion of nucleic acid contained in the various forms of nucleoproteids thus far

⁹⁴ Marie: Bulletin et Mémoires de la Société Médicale des Hôpitaux de Paris, p. 136, 1893.

⁹⁵ Chittenden: Boston Med. and Surg. Journal, August 20, 1896.

studied, we find exceedingly great variations in the amount of this acid present in the molecule: a fact which may be taken as evidence of the large number of molecular combinations present in the protoplasm of different cells. Thus, from the kidneys we obtain a nucleoproteid with only 0.37 per cent. of phosphorus, while, as representing *the other extreme*,⁹⁶ we have in the pancreas a nucleoproteid containing 4.71 per cent. of phosphorus and *in the lymphoid cells of the thymus a corresponding body with 3.5 per cent. of phosphorus.* . . . The very nature of the many bases which come from the cleavage of the nucleic acids outside the body; the ready convertibility of these bases into other allied bodies *by oxidation and reduction*; their own physiological action, which, though mild, is marked; the possibility—nay, the probability—that many other catabolic products may be obtained from these nucleic acids, and, further, that still other nucleic acids at present undiscovered may exist in the cell-protoplasm, all offer good reasons for believing that the nucleins and nucleoproteids, which are the most prominent constituents of the protoplasm of all cells, are the most probable antecedents of the internal secretions.”

There is evidently a sound foundation for the belief that phosphorus is the active constituent of the thymus gland. If thyroid extract failed to improve the mental condition of the ten cases collected by Cabot notwithstanding the increased growth witnessed, it is either because the thymic gland in all was structurally unable to respond to the increased oxidation which the stimulated adrenals induced or because no thymus gland was present. That this gland is absent in the vast majority of weak-minded, but not myxœdematous, children is shown by the researches of Bourneville and Katz. That phosphorus is the main specific constituent of brain- and nerve-substance is a recognized fact fully sustained by physiochemical data. That thyroid gland does not improve non-myxœdematous idiocy or weak-mindedness in children owing to the absence of phosphorus in the organism is shown by the corresponding effects it has on the skeleton of some cretins, as observed by Telford-Smith, the bones, by their softness, show-

⁹⁶ All the italics are my own.

ing the absence of the hardening that calcium phosphate procures. Finally, that the adrenals, through the normal oxidation processes insured by them when adequately stimulated by the thyroid secretion, sustain the activity of the thymus up to its proper standard is shown by the experiments of Hofmeister and Eisenburg, in which removal of the thyroid of various—herbivorous—animals caused bending of the legs. The thyroid is thus able to stimulate the adrenals, and the adrenals in turn can stimulate the thymus. But does the thymus *physiologically* stimulate the adrenals?

The fact that the thymus gland is but a temporary structure, one calculated to atrophy when its functions as a building organ are accomplished, would seem to suggest that stimulation of the adrenals is not one of these functions. If the deductions herein submitted are sound, it would appear to stand prominently as a bone-forming organ and *general phosphorus- or rather nuclein- purveying organ* from the time of the completion of its lymphadenoid elements during intra-uterine life until the final elaboration and growth of all tissues, including the skeletal frame-work,—i.e., around the period of puberty,—its powers gradually receding as permanent organs are developed. This conception of its purpose does not appear to have suggested itself to anyone so far, but it is quite in keeping with the collateral observations of a number of the best of modern embryologists.

One of the sources of leucocytes, as is well known, is the bone-marrow. In the process of bone-formation during foetal life, the first points of ossification appear during the second month, but it is only during the fourth that the development becomes markedly active on all sides. That the most active work of the thymus is performed during intra-uterine life is generally recognized; this, therefore, coincides with its most active bone-forming period. It seems reasonable to conclude that so important a function as leucocyto-genesis should not devolve upon structures undergoing formation, and also that the bone-forming organ should be intrusted with the function which ultimately would constitute the main active attribute of their product. Bone-marrow being the main leucocyte-forming structure, we should therefore expect the thymus to

assume this rôle until the bone-marrow had reached its normal physiological development.

Kölliker has always maintained that the formation of leucocytes was a function of the thymus: a position in which he has been sustained by Prenant and Oscar Schultze. J. Beard⁹⁷ took up the question and studied it with considerable care in the *Raia batis*, the smooth skate. He ascertained that the absence of leucocytes in the earliest period of embryonic blood in vertebrates persists until the first ones are formed within the thymus epithelium and from its epithelial cells. In embryos from twenty-eight to forty-two millimeters long the formation and emigration of leucocytes from the thymus becomes very active, and at this time there is no part of the embryo, including the blood, that is not infiltrated with leucocytes. This happens before lymphoid structures are developed elsewhere within the body of the smooth skate. Beard believes, with Kölliker, that the formation of leucocytes is a function of the thymus gland, and "the first leucocytes arise in the thymus from its epithelial cells; thus it is the parent-source of all leucocytes of the body": a conclusion which is further sustained by what appears to me to be a warranted deduction: *i.e., that the thymus is the main organ upon which the osseous, cerebro-spinal, and nervous systems depend, and perhaps all other tissues, for their organic phosphorus during their development.*

We have also seen that leucocytes are included among the bodies that contain phosphorus. The identity of the thymus as a bone-forming organ is apparently contradicted by Svehla's observation that fœtal thymus proves inert experimentally; but when we recall the fact that it only assumes its function the fourth month, that its inordinate activity may cause it to fix but little of the element itself, there is ample room for doubt as to the value of the experiments. If these facts do not prevail, all the data submitted, the recognized intra-uterine supremacy of the thymus over other glands, Chittenden's analysis, and several physiologically established facts would also have to be considered wrong.

All this entails the conclusion that thymus might prove an exceedingly valuable therapeutic agent in properly selected

⁹⁷ J. Beard: *Lancet*, Jan. 21, 1899.

cases. In fact, it seems possible that, in the very cases treated with thyroid extract referred to by Cabot, the addition of thymus might have caused the improvement in the mental condition which thyroid alone failed to procure. The absence of the thymus in Bourneville's cases supplies a firm foundation for this thought. Though some benefit has been obtained from sodium phosphate, it seems reasonable to believe that in physiological combination, as it occurs in thymus, phosphorus will prove far more efficacious. Whether it enhances suprarenal activity through this element or, as does thyroid, through a specific physiological body intended for this special purpose, matters little. It also stimulates the adrenals, and if we do not lose sight of the fact that the *entire cerebrospinal axis and the nervous system* utilize phosphorus as an all-important specific source of energy, and associate with this the enhanced oxidation which its stimulation of the adrenals procures, we cannot but realize that its intelligent use may insure results unattainable through any other agency. The benefit obtained by Owen in a case of paralysis agitans shows that these are not vain words. Indeed, we must not overlook the fact that impaired adrenal activity reduces the nutritional standard of *all* structures and that all cells fail to appropriate through the reduced metabolism involved their physiological constituents. While, therefore, paralysis agitans should not be classed as a nervous disease, it is nevertheless true that the nervous system, if the adrenals underlie the whole trouble, also suffers from impaired nutrition, and that phosphorus, its source of intrinsic energy, is as necessary to it as oxygen itself. *The benefit obtained from the therapeutic use of thymus gland is mainly due to the phosphorus-laden nucleins it contains.*

A number of authors have suggested that thymus was able to compensate for the adrenals. In Boinet's experiments in rats, for example, eleven out of fifty which had survived some time adrenalectomy showed hypertrophy of the thymus. Auld observed the same phenomenon in four cats, though he had removed but one adrenal in these animals. Pansini and Bonenati, Wiese, Hedinger,⁸⁸ Hart,⁸⁹ and others have also observed

⁸⁸ Hedinger: Verhandl. d. deutsch. path. Gesellsch., B. xi, S. 29, 1907.

⁸⁹ Hart: Wien. klin. Wochenschr., B. xxi, S. 1119, 1908.

hypertrophy of the thymus in subjects who had died of Addison's disease,—a condition in which, as is well known, the functions of the adrenals are arrested by organic disease. But hypertrophy does not always indicate a compensative function, especially when any of the ductless glands are in question. Those so far reviewed, the thyroid and adrenals, are intimately concerned, we have seen, with the destruction of toxic wastes. It follows, therefore, that removal of either set of organs allows such wastes to accumulate in the blood, and, as is well known, to raise the blood-pressure. This in itself is sufficient to produce hyperemia and congestion of the thymus with enlargement similar to that witnessed in the adrenals under the influence of many poisons. The enlargement of the thymus should not, therefore, be regarded as compensative.

What the evidence available does seem to warrant, however, is that the thymus sustains the functional activity of the adrenals by contributing what it contributes to all other organs, *i.e.*, the excess of phosphorus-laden nucleins required by the organism during its development, *i.e.*, until puberty. But we must not overlook the fact that what I mean by "organ" here includes its nervous system: the center and its efferent and afferent paths to the organ and its intrinsic nerve supply, vascular and glandular, to which phosphorus is, with the adrenoxidase circulating in the axis-cylinders, nerve-fibers, etc., as will be shown in the next chapter, a *sine qua non* of functional activity, as I have shown. It follows under these conditions that insufficiency of the adrenals or of the thymus must produce morbid phenomena similar, though less marked in degree, to those of the thyroparathyroid apparatus and the adrenals, all concerned also directly, we have seen, with nuclein metabolism and oxidation.

The participation of the secreting organs of the adrenal system in the functional relationship with the thymus is well shown in a case of marasmus carefully studied by R. L. Thompson,¹⁰⁰ in which "in addition to changes in the thymus extreme atrophy was found in the thyroid, parathyroids, and medullary suprarenals." Having had the opportunity to examine the thymus in 20 cases of marasmus at St. Ann's Asylum, in infants from birth to 1 year of age, he found in every case "a

¹⁰⁰ Thompson: Amer. Jour. Med. Sci., Oct., 1907.

notable atrophy of the thymus gland." So marked was the evidence in this and other cases referred to, sustained by contributory collateral data, that Thompson concludes that "all infants dying of marasmus exhibit marked atrophic changes in the thymus gland."

The important rôle I ascribe to the thymus, *i.e.*, to supply phosphorus in organic combination to all tissue, accounts for the morbid influence of atrophic changes in the thymus upon the organism which the "marasmus" portrays, in the light of the above facts, since, by causing atrophy of the thyroid, parathyroids, and adrenals, it inhibits the functions of the identical organs which, as I have shown, combine to sustain *oxidation, metabolism, and nutrition*. Though unable to account for the manner in which it exercised so potent an influence on the body at large, Friedleben, as long ago as 1858, stated that "the size and condition of the thymus was an index to the state of nutrition of the body," an observation confirmed, as stated by Thompson, by a number of investigators, among whom he mentions Mettenheimer,¹⁰¹ Stokes, Ruhrah, Rohrer,¹⁰² and Dudgeon,¹⁰³ who all noted that "atrophy of the thymus gland in children and wasting of the tissues go hand in hand," Dudgeon stating, moreover, that atrophy of the thymus gland was "the most characteristic lesion found in cases of marasmus."

On the whole, the above evidence seems to me to suggest:—

1. *That the function of the thymus is to supply an excess of phosphorus in organic compound as long as the development and growth of the body, particularly its cerebrospinal and osseous systems, demand it.*

2. *That impairment of the functions of the thymus underlies some of the disorders of nutrition which inhibit the development of the cerebrospinal, nervous, and osseous system during infancy, childhood, and early adolescence.*

3. *That certain diseases of nutrition in children and adolescents, especially marasmus, rachitis, and trophic disorders of the brain and nervous system, are due, in part, to impairment of the functions of the thymus.*

¹⁰¹ Mettenheimer: *Jahresb. f. Kinderheilk.*, Bd. lxxvi, S. 55, 1897.

¹⁰² Rohrer: *Amer. Jour. Med. Sci.*, vol. cxxiv, p. 847, 1902.

¹⁰³ Dudgeon: *Jour. Path. and Bact.*, vol. x, p. 173, 1906.

THE CIRCULATION OF ADRENOXIDASE IN THE NERVOUS SYSTEM.

We have now seen that adrenoxidase—the oxidizing body of the blood derived originally from the adrenals—takes part in the functions of the many organs reviewed, in so far as their supply of oxygen is concerned. That this applies to all organs there can be no doubt. Of the whole series, however, one, the nervous system, including the cerebro-spinal system and all ganglia and nerves, is the most complicated by far. It must, therefore, receive due attention to ascertain whether it also depends for its oxygen upon the adrenals. We shall see under the next heading that such is the case, and, moreover, that the large proportion of phosphorus which many of its components: the white substance of Schwann, the lecithin, etc., contain, brings it essentially within the reach of the thyroparathyroid secretion, *i.e.*, the thyriodase. The adrenoxidase and the thyriodase constituting the two active agents of the adrenal system, we shall be able, moreover, to realize why the nervous system is so manifestly involved in the diseases of the ductless glands.

Again, I would call attention to the fact that, while Harvey revealed to us the circulation of the blood in practically all organs, the one exception in his epoch-making discovery was the nervous system, and for obvious reasons: Its histology, the identity of the nerve-cell, and staining methods capable of bringing it to view were unknown in his time. The explanation of the circulation in the nervous system (apart, of course, from its known nutrient vessels, which are, in reality, external to the nerve cells *per se*) submitted in the next chapter, an amplification of that published in 1903 in the present work, is, I believe, the first effort of the kind in which histo-chemical data—and not mere assumptions—are the basis of analysis. The adrenoxidase, or oxidizing substance, is shown to circulate in the neuraxons, or axis-cylinders of nerves. If the reader will ask himself: How does the neurotoxin of tetanus, shown by Marie and Morax, Meyer and Ransom, and others to ascend in the axis-cylinders of nerves, perform this feat? he will conclude that circulation in these elements, as I interpret it, alone accounts for the phenomenon.

CHAPTER X.

THE POSTERIOR PITUITARY AS A GENERAL NERVE-CENTER AND AS CO-CENTER TO THE ANTERIOR PITUITARY IN SUSTAINING LIFE.

THE IDENTITY OF THE LOWER BRAIN.

IN the foregoing chapters, I urged that certain centers in the medulla oblongata were probably but subsidiary centers which received nervous impulses from the pituitary body by way of the tuber cinereum and other basal structures. I held, moreover, that "inhibition" as obtained by physiologists represented a pathological phenomenon in that it was caused by excessive constriction of the cardiac arterioles provoked by vasoconstrictors contained in the nerve stimulated, the vagus.

As is well known, it was the work of the brothers Weber (1815) which first suggested that the heart could be "inhibited" by stimulation of a definite region in the medulla. Their experiments differed from those we have reviewed in that the tissues of the base of the brain were traversed by the current, thus exciting structures in which we have seen sympathetic and other nerves pass from the pituitary to the bulb. One pole having been placed in the nasal cavity of a frog and the other on the spinal cord over the fourth or fifth vertebra, the heart's action momentarily ceased, then gradually resumed its normal activity. Approximation of the poles upon the cerebral hemispheres and stimulation of the cord produced no effect upon the heart. "Not until the medulla oblongata between the corpora quadrigemina and the lower end of the calamus scriptorius was stimulated," says William T. Porter, "did the arrest take place. Cutting away the spinal cord and the remainder of the brain did not alter the result." The level of fibers from structures below the brain is also suggested by the effects of experimental injury of the bulbar area which Flourens termed *le nœud vital*.

Galen had already noticed that death ensued when a certain spot in the floor of the fourth ventricle close to that which is now known as the center of the vagus was injured. But Legallois and Flourens have added much to our knowledge of its physiological relations, and the spot in question, as we have seen, is still considered as the respiratory center. "The results of various investigations -show, however," says Reichert,¹ "that Flourens's area, as well as certain other parts of the medulla oblongata that have been looked upon by others as being respiratory centers, are not such, but are largely or wholly collections of nerve-fibers which arise chiefly in the roots of the vagal, spinal accessory, glosso-pharyngeal, and trigeminal nerves, and which, therefore, are probably nerve-paths to and from the respiratory center. Moreover, excitation of the '*nœud vital*' does not excite respiratory movements, but simply increases the tonicity of the diaphragm; nor is the destruction of the area always followed by a cessation of respiration. While the precise location of the center is still in doubt, there is abundant evidence to justify the belief in its existence in the lower portion of the spinal bulb." That we are again dealing with the aggregate of centers to which the pituitary body projects its fibers suggests itself. Flourens located his "vital knot" in an area five millimeters wide *between* the nuclei of the vagus and spinal accessory nerves—again in the *lower end of the calamus scriptorius: i.e.,* a region comprised in the area to which the Weber brothers applied one electrode, the other being in the nose, when cardiac arrest or inhibition was first observed by them.

An interesting relationship seems to me to exist between these two sets of experimental results. Indeed, the area to which the pituitary body sends its fibers thus becomes the source of antagonistic effects involving the same structures: *i.e.,* the Weber brothers caused arrest of the heart by causing undue constriction of its coronaries and ischemia of the myocardium, in the manner previously described, while the lesion produced by Flourens in the same area, when sufficiently severe, blocked the flow of impulses to and from the heart. Flourens's *nœud*

¹ Reichert: *Loc. cit.*

vital, therefore, is no more the respiratory center than the area traversed by the current can be called an "inhibitory" area. We are simply dealing with the results of two morbid factors: overstimulation (Weber) and interruption (Flourens) of physiological—and therefore functional—impulses transmitted *through* the medulla and the cord.

In the fifth chapter reference was made to the fact that the posterior pituitary lobe alone, as shown by Howell, contained an active principle. This lobe, the "infundibular," has long been termed the "neural" portion of the whole organ, and appears to me to present anatomical features that further suggest a direct connection between it and the cerebro-spinal centers. Hence the use of the words "physiological impulses transmitted *through* the medulla and the cord." The question becomes all the more worthy of a searching inquiry, inasmuch as a casual examination of the mutual relations, anatomical and physiological, of the cerebral structures traversed by the current in the experiment of the Weber brothers suffices to show that the elements thus submitted to excessive stimulation coincide with those which would normally fall under the influence of the posterior pituitary body.

The physiological characteristics of the parts influenced by the current must first be ascertained. In the frog, the distance between the nose and the medulla being very short, a current would implicate all elements in its direct path, considering the character of the structures traversed. In this animal, the lizard, etc., the nasal nervous terminals, the tissues about the floor of the median ventricle and the habenula, appear to me as the paths that would be involved. In man the distance between the olfactory area or the nasal subdivisions of the fifth pair and the medulla is also relatively limited, and the intervening structures are of such a nature as to also allow the current to pass uninterruptedly in a straight path. But the floor of the median or third ventricle, which in its anterior portion overlies the base of the skull and is very thin, becomes what appears to be the inevitable path of free conduction, owing to this proximity of the olfactory bulb and the trigeminal nasal terminals to the medullary centers. Of special interest here, however, is the fact that in man (and to a great extent in the

frog) the first structure reached by the current after the nasal structures would be the infundibular portion of the third ventricle: *i.e.*, that connected with the posterior pituitary lobe. Again, and very suggestive, is the fact that these structures and all those falling in the line of the current form part of what Professor Foster terms "in point of origin the oldest part of the brain" and "the central gray matter" which "seems to serve chiefly as a bed for the development of the nuclei of the cranial nerves." Indeed, we might repeat that, as stated by Reichert,² "one center has been located in the rabbit in the *tuber cinereum*, which has been named a polypnoëic center because, when excited, the respirations are rendered extremely frequent." . . . "Another area has been located in the optic thalamus, in the floor of the third ventricle; this center," says the author, "is believed to be excited by impulses carried by the nerves of sight and hearing, and when irritated causes an acceleration of the respiratory rate."

The more dorsal portion of the current would strike a no less important physiological region. "Next to the central gray matter," says Professor Foster, "and more or less associated with it, comes what is called the tegmental region, of which the reticular formation coming into prominence in the bulb and continued on to the subthalamie region forms, as it were, the core. Belonging to the tegmental system are numerous masses of gray matter from the conspicuous optic thalamus and the red nucleus in front to the several nuclei of the bulb behind. This complex tegmental system, which may, perhaps, be regarded as a more or less continuous column of gray matter, comparable to the gray matter of the spinal cord, serves as a sort of *backbone to the rest of the central nervous system*."

The morbid effects of the current become normal consequences when we consider that the structures traversed by it include those that even emotions will disturb. Referring to the posterior portion of the pons, that adjoining the tissues that form the fourth ventricle and which represents the downward continuation of the tegmentum, Professor Duval says: "It is, indeed, to the pons that we seem to be authorized to

² Reichert: *Loc. cit.*

attribute the most important rôle in the greater emotional expressions, laughing and weeping, cries of pain: in a word, involuntary manifestations." That the structures such as those penetrated by the current should be suddenly jarred and forcibly thrown into vibratory conditions entirely foreign to their normal vibratory rhythm is manifest. That such jarring, especially when the current follows axially a direction opposite to that of a physiological stream of impulses, should so pervert its normal influence upon the organs to which these impulses are normally distributed—heart, lungs, stomach, etc.—as to temporarily or permanently arrest their functions is **not** only logical, but in accord with the known effects of electricity upon the more highly developed structures.

And we can also doubtless better understand why respiration still continues very much as usual after removal of the brain above the medulla, and why, indeed, all nervous manifestations other than ideation can persist after such mutilation. While there is no "*nœud vital*," or gauglion of life, in the sense given these words by Flourens,—*i.e.*, in the spot of the medulla where injury arrests respiration,—and the area so injured is not "the mysterious seat of the unknown principle of life," there is, nevertheless, in this location, not a *locus minus resistentiæ*, but an aggregation of nervous paths from all directions, which an injury can functionally impair or destroy, according to the quantity of tissue involved and the kind of lesion produced. Flourens doubtless caused death; but in looking for death in his experimental animals he doubtless did not treat the "*nœud vital*" with the gentleness of a dove. Death ensued—the result of conditions similar to those produced by the Weber brothers with electricity in the sense that molecular disturbance was produced. Yet the Weber brothers only jarred the naso-bulbar structures, and produced temporary inhibition of cardiac action; being more diffuse, the current spread over greater bulbar surface and did less injury. Flourens's puncture, on the contrary, produced an organic lesion, capable not only of destroying the tissues involved, but also of annulling, by the circumferential compression of the neighboring elements caused, the functions over which the latter preside. Even the process of repair, which at once begins under such

conditions, may lead to a fatal issue, the infiltration throttling, as it were, the paths *to* and *from* organs through which life is sustained. When we consider the small relative size of the fourth ventricle, and the fact that the so-called "vital knot" is located in an area which may be computed only by a few millimeters; when we furthermore recognize that such an injury would thus include the vagal, spinal accessory, glosso-pharyngeal, and hypoglossal within its radius of morbid influence, death as an injury to the spot becomes a normal consequence. The heart and the entire respiratory system—to refer only to those directly concerned with life's processes—are the mechanisms first functionally arrested.

* And yet while obstruction of these few square millimeters of bulbar elements will rapidly destroy life, it is possible, says Professor Foster, in the case of some animals "to remove the cerebral hemispheres and to keep the animal not only alive, but *in good health* for a long time—days, weeks, or even months after the operation!"

There must prevail in this connection, however, another contradictory interpretation of experimental phenomena. Indeed, how can we reconcile the presence of motor *centers* in the cerebral cortex with the ability of an animal from which both hemispheres have been removed to execute the motions ascribed to these areas? That an animal deprived of its hemispheres will do this is graphically shown in the following lines of Professor Foster's: "We may, perhaps, broadly describe the behavior of a frog from which the cerebral hemispheres only have been removed by saying that such an animal, though exhibiting no spontaneous movements, can by the application of appropriate stimuli be induced to perform all, or nearly all, the movements which an entire frog is capable of executing. It can be made to swim, to leap, and to crawl. Left to itself, it assumes what may be called the natural posture of a frog, with the forelimbs erect, and the hindlimbs flexed, so that the line of the body makes an angle with the surface on which it is resting. When placed on its back, it immediately regains its natural posture. When placed on a board, it does not fall from the board when the latter is tilted up so as to displace the animal's center of gravity; it

crawls up the board until it gains a new position in which its center of gravity is restored to its proper place. Its movements are exactly those of an entire frog except that they need an external stimulus to call them forth." It is quite clear that all motor phenomena are carried out, notwithstanding the absence of parts of the brain which have been undeniably shown by experiments in animals, pathological conditions of the human hemispheres, etc., capable of inciting them. The familiar convulsive movements in various parts of the body trunk, leg, arm, etc., when certain motor areas are stimulated would mean nothing to us if the use of electricity for this purpose were the basis of this doctrine, but *lesions* in these areas have unquestionably proven that they do preside over motor functions, not only in a general way, but in the sense implied by "cerebral localization." How account for the self-evident discrepancy which the entire absence of these structures indicates in present conceptions of the processes involved?

We are brought nearer to a solution when the removal of cerebral tissues—those to which I have referred as jarred by the electric current passed by the Weber brothers between the nose and the bulb—is continued downward until the cord only is left. "Very marked is the contrast," says Professor Foster, "between the behavior of such a frog which, though deprived of its cerebral hemispheres, still retains the other parts of the brain, and that of a frog which possesses a spinal cord only. The latter when placed on its back makes no attempt to regain its normal posture; in fact, it may be said to have completely lost its normal posture, for even when placed on its belly it does not stand with its forefeet erect, as does the other animal, but lies flat on the ground. When thrown into water, instead of swimming it sinks like a lump of lead. . . . When a board on which it is placed is inclined sufficiently to displace its center of gravity it makes no effort to regain its balance, but falls off the board like a lifeless mass." Such a frog moves its limbs irregularly, but one has but to witness such motions to at once conclude that they are aimless, mere random expressions of the inherent power to contract possessed by all muscular tissues, and which even persist some time after death, especially in the case of

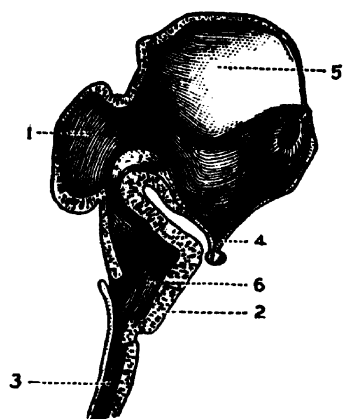
the heart-muscle. Very marked is the contrast, indeed, between this animal and one still endowed with the tissues of the base of the brain. "Pigeons, for instance, have been kept alive for five or six weeks," says the same author, "after complete removal of the cerebral hemisphere with the exception of portions of the crura and corpora striata immediately surrounding the optic thalami." . . . "In warm-blooded animals, as in the more lowly cold-blooded frog, the parts of the brain *below or behind* the cerebral hemispheres constitute a nervous machinery by which *all the bodily movements* are carried out."³

That this mechanism is located below the hemispheres in man has also been illustrated by many cases reported, among which may be cited the famous crow-bar case, in which, "by a premature explosion of gunpowder, an iron bar three and a half feet long, one and a quarter inches in diameter, and weighing thirteen and a quarter pounds, was shot completely through a man's head, and perforated his brain. This man walked up a flight of stairs after the accident, and gave his account of how it happened. Although his life was naturally despaired of for some time, he *developed no paralysis*; nor did marked impairment of his intellectual faculties follow convalescence. Eventually he recovered his health. Twelve years elapsed before his death, during which time he was a laborer on a farm."⁴ This pointedly suggests that while the cerebral hemispheres from the lowly frog to the highest mammal can only awaken motion through volition, *i.e.*, voluntary movements, *the base of the brain—the pituitary body as we will see—can automatically govern motion through the intermediary of spinal gray matter.*

A remark which in this connection is of particular interest to us is that of Professor Duval, when, referring to the meaning of bulbar functions, according to modern conceptions, he says: "For the physiologist, the medulla extends above the limits of the vertebral column into the cranium *and about up to the sella turcica.* " *I would say into the sella turcica, for it seems clear to me that the posterior pituitary lobe presents*

³ The italics are my own.

⁴ A. B. Ranney: "Lectures on Nervous Diseases."



MEAN AND VERTICAL SECTION OF A THREE
MONTHS' EMBRYO. [*Dejerine.*]

1, Aqueduct of Sylvius. 2, Medulla Oblongata. 3, Central Canal. 4, Infundibulum and Pituitary Bodies [the latter have been added to the original]. 5, Optic Thalamus. 6, Fourth Ventricle.

the functional characteristic that would fulfill the requirements of the complementary processes that the functions of the hemispheres demand.

The annexed colored plate, which represents a median and vertical section of the encephalon and bulb of a three months' embryo, distinctly indicates the direct continuation of the cord up to the posterior or infundibular pituitary lobe. The tract connected with the posterior pituitary is colored bluish gray. The pituitary has been added to the infundibular extremity of the original illustration. The relations of the structures which ultimately become the corpora quadrigemina by meeting the posterior part of the third ventricle are well shown.

That my views in this connection are based on a solid foundation is further sustained by the painstaking investigations of Andriezen,⁵ who traced a direct connection between the pituitary and the medullary and other more anterior structures through the various phylogenetic stages of vertebrates. The following statements and the table appended are quoted from his paper: "A survey and investigation based on all classes of vertebrates show that the hypophysis occupies the position and relationship to the other structures which may be condensed in the following table:—

"RELATION OF PITUITARY TO OTHER NERVE-CENTERS AND HEAD-STRUCTURES IN ORDER FROM BEFORE BACK."

<i>Nerve-center.</i>	Olfactory center.	Posterior lobe of pituitary.	The bulbo-spinal centers.
<i>Nerves.</i>	Olfactory nerves.	Hypophyseal nerves.	Bulbo-spinal nerves.
<i>Distribution.</i>	Epithelium of nasal sac.	Pituitary duct gland (anterior lobe).	Buccal, etc., and general subcutaneous.
<i>Body-region.</i>	Pre-oral (prostomial).	Oral.	Post-oral (branchial, etc.) and general body."

⁵ Andriezen: *British Medical Journal*, Jan. 13, 1894.

Of course, this applies to both pituitary bodies, but I have shown that the anterior lobe could originate motor impulses in the partition separating it from the posterior lobe, and transmit them via the latter, the basal tissues, the bulb, the cord, the sympathetic chain and finally the splanchnic nerve to the adrenals. That the investigations of Andriezen, though sustained by the previously recorded results of removal of the pituitary by Vassale and Sacchi,^{5a} should have borne but little fruit, so far, is probably accounted for by his statement that "variations in weight bring it under the Darwinian law of panmixia; if so, the indication being, what study of lower vertebrates shows, namely: that it has probably passed the acme of its activity and in man is functioning less vigorously."

I must express the belief, however, that, when man is in question, cessation of natural selection may not always mean that an organ has become useless, but instead that it has reached the acme of perfection. Loss of functional vigor may denote, in this connection, what it denotes in the human hand as compared to that of the gorilla: *i.e.*, gain in functional precision and delicacy.

In the embryo, the posterior pituitary body opens directly *into* the third ventricle through the infundibulum. If during uterine existence "the whole life-achievement of myriads of generations of living things" is represented, the phylogenetic history of this organ should show traces of its ultimate functions. Andriezen found that in the amphioxus its analogue is represented by "a subneural glandular organ, a duct lined by ciliated epithelium which affords a communication between the buccal and neural cavities, and a group of nerve-cells around and at the back of the upper opening where the duct widens into the ventricular cavity." We have here the main primitive structures of the pituitary in man.

Referring to Andriezen's investigations, Berkley⁶ says: "He has farther shown that particles of carmine, suspended in the water surrounding the animals, will be taken up with the water *passing through the infundibular duct* and carried by ciliary action *into the ventricle*, and thence into the *central*

^{5a} Vassale and Sacchi: *Rev. Sper. di Fren.*, p. 83, 1894.

⁶ Berkley: *Brain*, Winter, 1894.

canal of the cord; finally the particles of carmine may be traced right up to the free end of the canal, where the spinal cord opens into the exterior by the blastopore; therefore it is made manifest that the infundibular duct carries a stream of oxygen-bearing water for the nutrition of the tissues and the carrying off of their effete products." Alluding to personal studies to which I will presently refer, Berkley then adds: "It is quite curious to find essentially the same structures preserved in as high a vertebrate as the dog, and descending to so low a zoological order as amphioxus, though, as Müller remarks, the pituitary is practically the same *from myxine to man*." Yet in man the infundibular orifice is *closed*, and the posterior pituitary, during its evolution, must, therefore, have assumed some function other than that possessed by the organ during the earlier phases of its career and of which the earlier forms should also show traces.

We have seen that oxygenation of the blood, the highest development of the function carried out by the water-vascular system in the amphioxus, belongs to the domain of the anterior pituitary. The remaining inference afforded by the phylogenetic history of the organ, therefore, is, in my opinion, that *the group of nerve cells around and behind the upper opening which in Amphioxus and Amocetes forms the threshold of the oxygen-bearing water system is the prospective adrenal center in the human pituitary*, which center, we have seen, is also concerned with oxygenation.

I must state that I consider this perfect concordance between the functions of the anterior and posterior pituitaries as I have conceived them and those found throughout the entire evolutionary scale of zoological forms as far back as the amphioxus by Andriezen as very strong evidence that my views are sound.

HISTOLOGY OF THE POSTERIOR PITUITARY BODY.

What is the physiological relationship between the two lobes? Déjerine⁷ states that vertical and horizontal sections of both organs show that they are absolutely distinct and sepa-

⁷ Déjerine: "Anatomie des Centres Nerveux," vol. I, 1895.

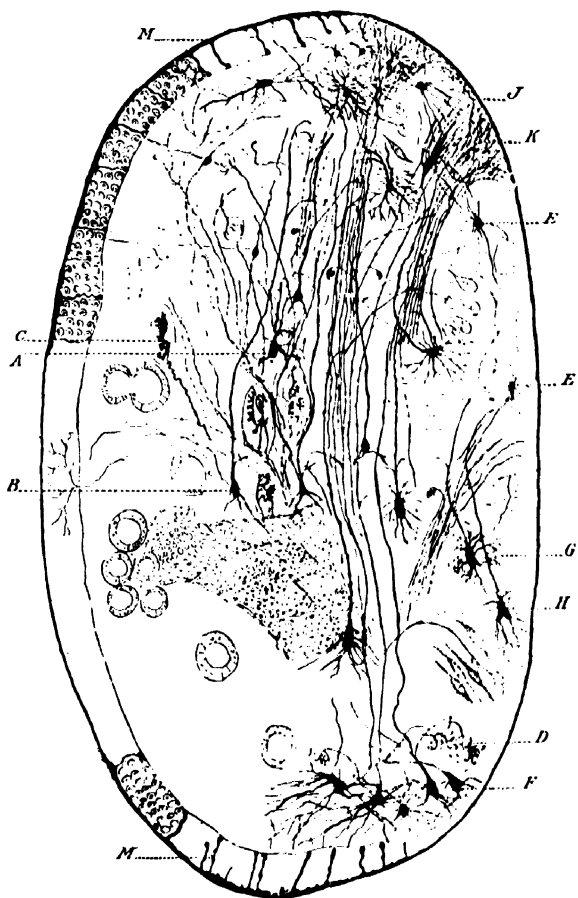
rated by a fibrous lamina; and, furthermore, that "the posterior lobe alone is connected with the infundibulum." . . . "It is developed from the brain" and "is a dependence of the middle ventricle." The anterior lobe is only connected with the cerebral structures through vessels which, according to Berkley,⁸ "directly pass into it from the *substance* of the infundibulum." The blood-supply of the posterior lobe is also derived from the same source, but it is less rich, though sufficiently so to satisfy the needs of an active function. Indeed, the organs differ mainly in the character and wealth of their nerve-supply—much to the advantage of the posterior lobe, however. The development of the anterior lobe from the ectoderm of the primary oral cavity, instead of, as in the case of the posterior lobe, from the embryonic brain, accounts for what anatomical dissimilarities prevail.

The histological characteristics of the posterior lobe also suggest that it is the seat of some nervous function of a high order. This is well illustrated by the exhaustive study by H. J. Berkley⁹ after an examination of some two thousand five hundred slides. A summary of such a work hardly does it justice; I must therefore refer the reader to the original paper for details other than those that I will presently submit.

The outer layer of the organ was found by Luschka and Müller to be composed of gray matter similar to that found over the infundibulum. Berkley refers to this layer as composed of slightly irregular *ependymal* cells three or four deep, through which rather thick ball-tipped filaments penetrate to the second anatomical subdivision of the lobe. This outer coating of cells does not extend around the entire lobe, however, but covers only its free, or posterior, surface. Its anterior portion, that nearest the partition between the two lobes, has no such covering, so that its elements appear to be in contact with the partition itself or to be only separated from it by its capsule. The second subdivision of the posterior organ occupies, judging from Berkley's drawings, about one-third of its mass, and recalls, as to structure, that of the anterior lobe.

⁸ Berkley: *Brain*, Winter, 1894.

⁹ *Ibid.*



VERTICAL SECTION OF THE POSTERIOR PITUITARY BODY. [Lateral.]

Somewhat diagrammatic to indicate various types of cells.
Its normal size is that of a small pea.

[Brain.]

Again do we find the closed glands, or alveoli, including the colloid substance. Again are the glandular elements supported by connective-tissue trabeculae permeated with capillaries, though the caliber of the larger vessels is somewhat smaller. Yet—a feature which seems to me important—the colloid alveoli are always most numerous near the outer edge of the ependymal cells, that portion farthest away from the interlobular partition, while the space between these structures and the partition is occupied by cellular elements of an entirely different kind.

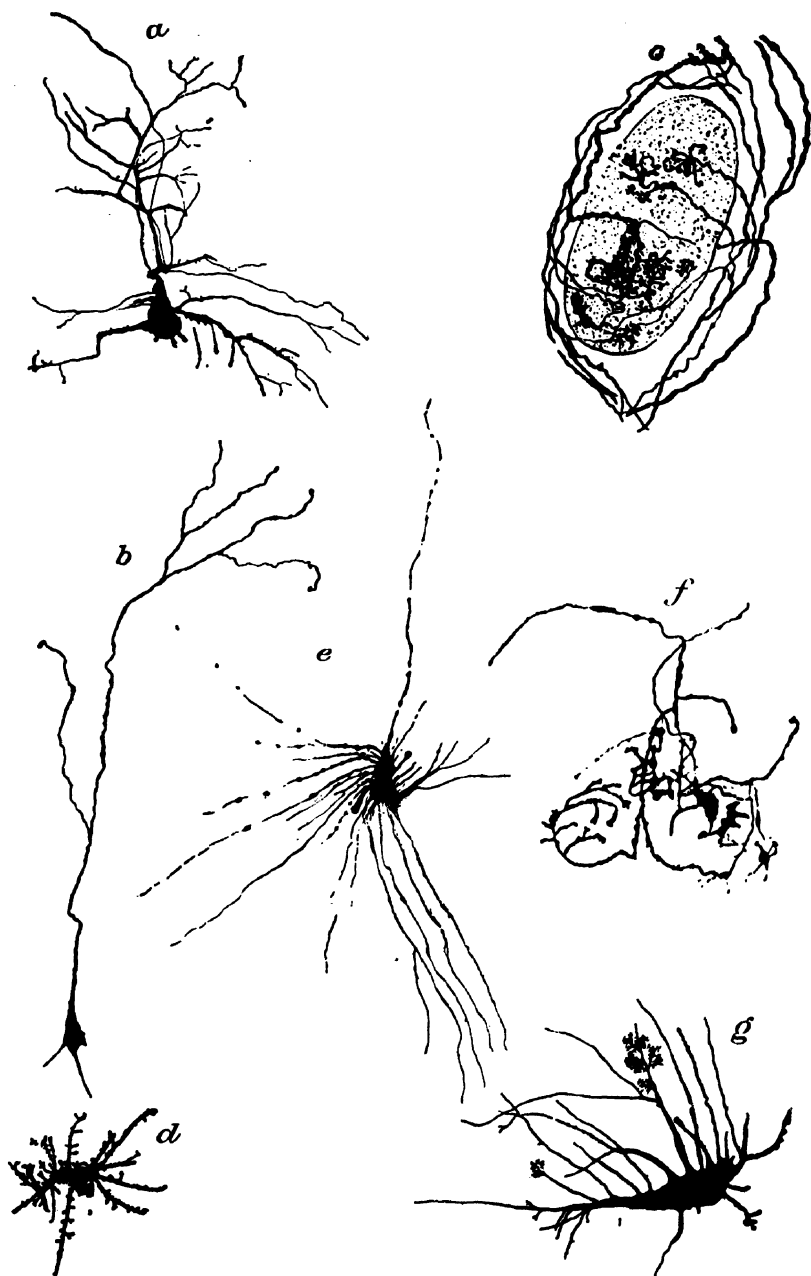
The third portion may be said to occupy nearly two-thirds of the entire lobe: a perfect maze of nervous elements, some of which have not so far been found elsewhere in the organism. Yet connective-tissue partitions carrying blood-vessels are discernible throughout this entire area: a feature which suggests that an orderly subdivision exists. Its nervous elements vary greatly in form, but they may be divided into three general classes: 1. Cells that give off protoplasmic extensions, neuraxons, etc., that are not sufficiently long to reach the upper, anterior region of the lobe: *i.e.*, the infundibular region. 2. Cells the extensions of which reach this region. 3. Cells that are found mainly or only in this portion of the organ.

The *first class* includes flask-like cells with knot-tipped fibers that recall those of the anterior lobe (Fig. A, Plate I, and Fig. a, Plate II). These bodies are widely distributed, but their multitude of ramifications end freely among neighboring structures. Similar, though smaller, cells (Fig. B, Plate I, and Fig. b, Plate II) are found chiefly in the center, and have processes that extend upward a considerable distance and there often terminate in a brush-like figure. In this class may be included peculiar oval bodies (Fig. C, Plate I, and Fig. c, Plate II), mainly found in the center of the organ, that recall closed follicles. They give off axis-cylinders that coil about them irregularly, and fibers which terminate either in irregular figures resembling combs with knob-tipped teeth or in cat-o'-nine-tail-like tufts. Neuroglia cells, especially those of the mossy kind, are shown in Fig. d, Plate II, while spider-cells (Fig. E, Plate I, and Fig. e, Plate II) are mainly found where the nerve-cells are very numerous: *i.e.*, the anterior third

of the lobe. The spider-cells, however, which only differ from those found in the cerebral tissues by their larger size in proportion to the length of their tentacles, outnumber the other cells as the upper infundibular region of the lobe is reached.

The cells included in the *second class* are all, as stated, distinguished by one or more protoplasmic extensions, which insinuate themselves between all the elements intervening between their starting-point and the infundibular area referred to, where they break up into figures. The lowermost of these, the ganglion-cells shown in Fig. *F*, Plate I, and Fig. *f*, Plate II, exemplify this type very well, since their extensions traverse the entire organ in an upward direction and end in the upper infundibular area. Higher up in the organ large pyramidal and oval cells are found (Fig. *G*, Plate I; Fig. *g*, Plate II, and *g*, Plate III), the terminal subdivisions of which break up into exceedingly fine feathery filaments. The only axis-cylinder of this cell, after distributing a few branches to neighboring elements, continues upward and subdivides, when near the upper margin of the infundibular region, into a complex net-work which entwines the alveoli found there. A third type, characterized by short dendrites and many hair-like processes (Fig. *H*, Plate I, and Fig. *h*, Plate III), is found throughout the entire nervous area and also gives off one long dendrite, which extends a long distance upward and forward; this extension may possibly reach the infundibular region or its neighborhood. Coming from every direction, these long dendrites seem, at any rate, to point all toward this one region. The other dendrites are short and distinguished by the presence of more or less numerous hairy processes, while some of the terminal ramifications are ball-tipped—suggesting a possible identity as collectors of energy, which, transformed in the body of the cell, are directed upward by the long dendrites.

In the infundibular region of the lobe—i.e., the cellular elements of the *third class*—the final ramifications of the long dendrites form an extremely complex aggregation of tufted figures, wavy threads, and feathery protoplasmic ramifications. In the midst of this maze of nervous elements certain cells are to be found, the like of which Berkley has not been able to detect in any part of the central or peripheral nervous system.



VARIOUS TYPES OF CELLS IN THE POSTERIOR
 PITUITARY BODY. [Berkley.]

[Brain.]

They are small and round, and give off strong dendrites, which appear knotted or covered with thorns, giving them a "prickly appearance" (Fig. *J*, Plate I, and Fig. *j*, Plate III). Another variety found in abundance in this region is a small cell with a rich, apical tuft of fine, wavy processes. They are also distributed in the midst of a net-work of varicose nerve-fibers (Fig. *K*, Plate I, and Fig. *k*, Plate III) in the upper and near the anterior border of the lobe "along the space formerly occupied by the infundibular duct." As already stated, the spider-cell is to be found in great abundance in this locality, which, added to the other two varieties of cell, gives us three main cellular elements as representatives of the class of cells found mainly or only in the upper infundibular region of the organ.

As already stated, I do not regard it as a secreting structure. The view that it produces an internal secretion is merely assumed. Howell found that, while an extract of the anterior lobe produced no effect, an extract of the posterior lobe caused a rise of the blood-pressure. Since then, also, considerable use of such extracts has been made in therapeutics. But the facts that these effects correspond admittedly with those of adrenal extract, that they give the adrenal reaction, and that the presence in the organ of chromaffin cells has been established suggest that we are not dealing with a secretion. In fact, in practically all animals, excepting the cat and dog, there is no connection with the third ventricle above.

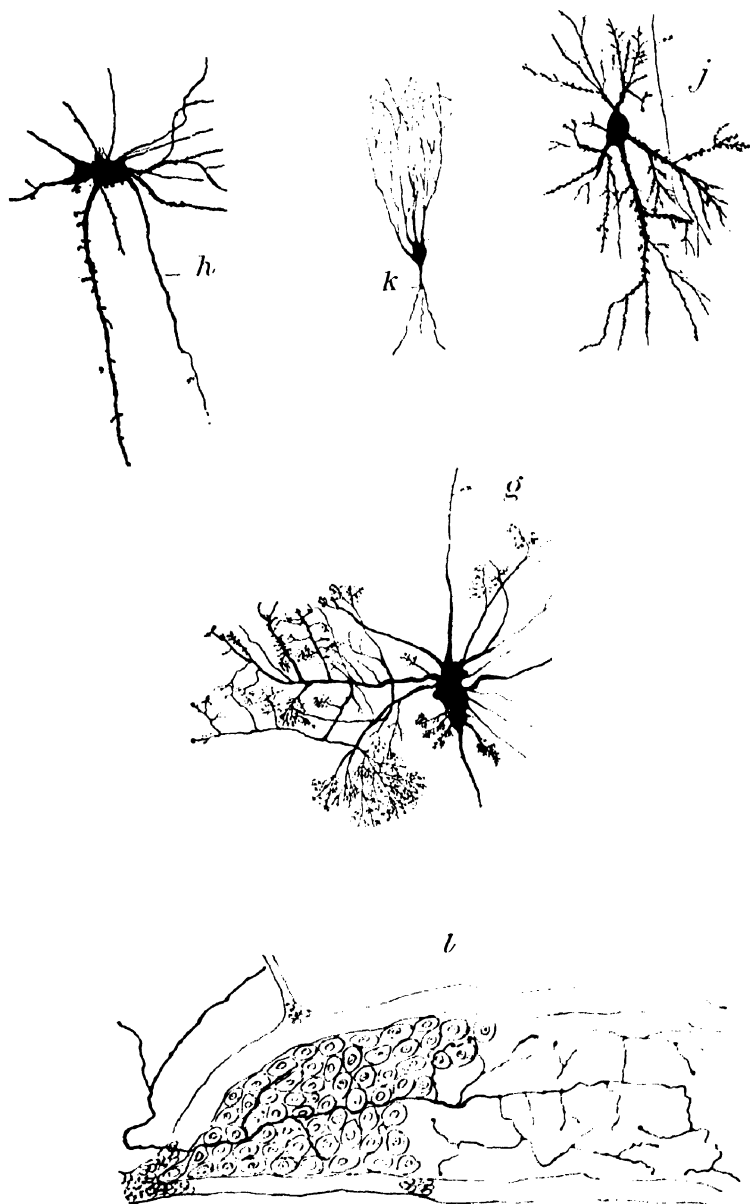
On the other hand, there is, we have seen, good ground for the belief that, as I pointed out in 1903, the posterior lobe is a general nerve-center, and that, through its nervous connection with the adrenals, it governs, besides, general oxygenation. That this view is gaining ground is shown by the recent statement of Lewin, of Berlin,¹⁰ that "the majority hold that the hypophysis is a ductless gland that has an influence over the nervous system or has something to do with the red blood-corpuscles."

And, yet, what is the connecting structure between the posterior pituitary body and the parts to which, under such conditions, its energy would be supplied? Berkley believes—erroneously we have seen—that none of the nervous elements

¹⁰ Lewin: quoted by Archibald Church, *Journal Am. Med. Assoc.*, July 10, 1909.

of the infundibular lobe itself pass beyond its limits into the infundibulum. His histological work shows that, while "all the axis-cylinder processes and the long dendrites have a general tendency upward and forward, both dendrites and neuraxons branching as they proceed onward, all traces of the dendrites of the inferior and median cells of the lobe are lost some little distance below the superior edge." After an allusion to the vessels and fibrillated tissues that connect the infundibulum with the posterior lobe, he says: "The whole arrangement of the structures of the infundibulum" is "here altered." Then, referring to both lobes, *i.e.*, the hypophysis, he remarks: "Elsewhere it shows no break in the described arrangement, the line of differentiation between hypophysis and infundibulum being sharply drawn, a layer of coarse connective-tissue bundles being placed between and separating the glandular and other structures of the pituitary from the tissues of the infundibulum." While the neural lobe is autonomous, Ramon y Cajal, Andriezen, Gentès and others have conclusively shown, as previously stated, that nerve-fibers passed from this lobe and the *pars intermedia* to the tuber cinereum and beyond.

Notwithstanding this striking autonomy of the organ, there are several features in its histological make-up that suggest an additional connecting-link between it and the infundibular structures. Berkley refers to the "outer lamina of slightly irregular ependymal cells (Fig. *M*, Plate I) three or four deep, arranged after the manner of the *cuticular epithelium*." This lamina, which older anatomists considered as a continuation of the ventricular gray substance, only covers, we have seen, the free portion of the posterior lobe and is not continuous with the infundibular ependyma. Again, "there are seen, extending from the thin capsule surrounding it" (here Berkley alludes to the *capsule* that surrounds the entire posterior lobe), "numbers of rather thick varicose threads, all unbranched, and invariably ending, when their terminations can be discovered, in a ball-shaped figure, at a definite line in the substance of the body, usually at the *inward* ending of the first layer of epithelial cells, at the line of separation from the more centrally situated elements. These knobby threads," he says, "strongly resemble the ependymal glia-cells of embryonic life, and possibly may be related to them; but, as their



VARIOUS TYPES OF CELLS IN THE ANTERIOR AND POSTERIOR PITUITARY BODIES. [Burkimp.]

Figs. h, j, k, and g: Cells in the Posterior Pituitary Body. FIG. l: Portion of Glandular Elements of the Anterior Pituitary Body.

[Brain.]

basal end is shrouded in a blackened aggregation of cellular masses, their histological origin must remain a matter of some uncertainty."

If, with these histological data before us, we examine Plate I, a suggestive fact asserts itself: *i.e.*, that the lamina of ependymal cells referred to forms a skull-cap-like covering for the posterior two-thirds of the posterior lobe. The glandular alveoli of the latter, with their colloid substance, are, therefore, in the best possible position for the reception of any nervous impulse that the ependymal cells may be able to transmit outwardly. This is emphasized in Plate I, which shows that this layer exactly covers the entire surface of the posterior region without reaching beyond its limits. The posterior surface of the posterior lobe thus seems to be held in the grasp, as it were, of its ependymal covering, which in turn contains the nervous, "rather thick, varicose threads." This suggests that the capsule may not be the insignificant structure it is now thought to be. Even the fragmentary data we have concerning it tend to indicate that it plays an important rôle in the functions of the organ.

Mere protective structures are usually detached without much difficulty from the underlying tissues. Berkley states, referring to the posterior body: "This lobe is so strongly adherent to the dura that it pulls out of the rest of the pituitary body in removing this with the brain, unless the membrane is dissected with it from the base of the skull." Since the capsule is the part of the lobe so strongly connected with the dura, it must as firmly adhere to the layer of ependymal cells beneath; otherwise efforts at removal would tear it away from the latter. This firm hold of the capsule on the cellular layer is fully accounted for by the thin, fibrous partitions the former sends through the latter, but this in itself suggests an intimate relationship between capsule and cellular layer, especially since the "blackened aggregation of cellular masses," referred to by Berkley, which form the basal extremities of the nervous "threads," all terminate in what appears to be, in his drawings, thickenings in the capsule proper. That such a relationship between the capsule and the nervous elements must exist is further shown by his reference, in the descriptive text of the

illustration, to the "capsule of the lobe thickened in places, *from which* extend threads that end in knobs," etc. That the varicose threads and the capsule are structurally continuous, the latter thus dipping, through a multitude of protoplasmic projections, into the deeper elements of the lobe is evident.

We have seen that many features suggest a relationship between the *anterior* pituitary and the adrenals, through nerves at present considered as appurtenances of the sympathetic system. That the anterior lobe contains but one kind of nerve connected with this function—besides its vasoconstrictors—is shown by the following statement of Berkley's: "In the glandular portion of the body, nerves, other than those belonging to the sympathetic system, are not found. They are very fine *varicose* fibers, with numerous ramifications and branchlets coming off from the main stems at a right or slightly obtuse angle." These fibers must, therefore, represent, considering their general morphology and location, not terminals of the connecting nerves and distributors of energy, but *collectors* of energy, *i.e.*, of sensory impulses. They are probably the fibers which Cajal traced to the floor of the third ventricle. If Fig. 1 in Plate III, which represents a section of the glandular portion of the anterior lobe, is consulted, it will be seen that these nerves present the two main characteristics of the capsular threads of the posterior lobe: *i.e.*, they are also varicose and their tips are likewise knobbed. Since, therefore, the nerves so disposed in the anterior pituitary are collectors of energy, *the varicose and knobbed threads of the capsules of the posterior pituitary must also be collectors of energy.* This is further sustained by the analogy between the two organs to which reference has already been made.

That a direct nervous connection between the posterior pituitary and the infundibular tissues, etc., exists by way of the capsule of the former is thus probable—thus making it possible for impulses generated in the depths of the lobe to reach the ventricular structures, irrespective of the sharply defined connective-tissue separation between the lobe proper and the infundibulum. Indeed, such a separation seems a necessity, inasmuch as an impulse, transmitted through the intermediary of the capsule must, owing to the skull-cap shape of the latter,

come from every part of the underlying structures and only reach the basal structures through paths that are continuous with the capsule's tissues, and irrespective of the nerves which arise directly from the two lobes and pass upward by way of the interior of the infundibulum. That a profuse padding of cellular tissue is Nature's resource under such conditions is well illustrated by the following remark of Déjerine's: "The vessels of the central nervous system are surrounded by two sheaths of a different kind: the *internal* is connective in nature and belongs to the mesodermic layer; the *external*, neuroglial in nature, is developed at the expense of the external, or ectodermic, layer." The capsule has been compared to the cerebral cortex, perhaps with justice, as we shall show.

Berkley, referring to the various cellular structures in the deeper portion of the lobe supplied with long extensions, says: "The axis-cylinder extensions of all the cells in the inferior portion of the lobe turn upward. . . . Those belonging to the larger proportion of the smaller cells of the superior border turn upward and intermingle with the marginal fiber net-work. . . . All the axis-cylinder processes and the long dendrites have a general tendency upward and forward, both dendrites and neuraxons branching as they proceed onward: but all traces of the dendrites of the inferior and median cells of the lobe are lost some little distance below the superior edge, and then the neurons only are intermingled with the extensions of the smaller superficial cells, passing them, however, before the border is finally reached, where they spread out into a most extensive fret-work of fine *varicose* fibers, still retaining something of their previous longitudinal arrangement from the threads of the uptending fibers being coarser than the lateral and intermingling branches. It is doubtful whether any of these fibers pass beyond the limit of the lobe into the infundibulum; our sections give no evidence of such an arrangement." This upward tendency of all cells, and the evident concentration of their functional activity at the upper extremity, seem to us to further emphasize the identity of the posterior lobe as a powerful source of energy. Its junction with the end of the infundibulum becomes, under these circumstances, the normal pathway for all the energy that the

organ can accumulate. Capsule and protoplasmic extensions or processes all serve a similar purpose, but the neck of the organ is its own functional limit.

We must not lose sight of the fact, however, that other nerves penetrate the organ. This is shown by the fact that Berkley says, in this connection: "the nerve-fibers accompanying the larger arteries are sometimes distinctly seen coming from the infundibular tract into the body of the posterior lobe of the gland and ramifying through it." That there is no connection between these and the nervous structures previously described, however, is shown by the additional statement: "Connections between the fibers of the vascular supply and the nerve-cells of the organ we have never been able to observe. That these are the nerves through which the organ receives its own functional energy—i.e., the impulses to its vessels and alveoli,—as in the case of other organs, is probable."

The prevailing view that the embryonal supporting substance of the brain and spinal cord, the ependymal neuroglia, almost entirely atrophies and disappears in the adult mammal would tend to counteract my belief that the capsule and its underlying structures are important factors of the posterior lobe's functions. Berkley, alluding to the writings of various observers in this connection, and referring to the infundibulum and other tissues of the third ventricle which he had just described, says: "After reading these statements, it was something of a surprise to find the above-described beautiful specimens of several types of ependymal neuroglia extending from *all portions of the middle and inferior regions of the cavity of the third ventricle* and reaching to the periphery, all portions, bodies, branches, tentacles, and subpial endings being readily distinguishable. The region examined is, therefore, very interesting not only from the great variety of neuroglia-cells that may be seen within a very limited area, but from the fact that varieties of the ependymal neuroglia-cells, *previously supposed to have entirely disappeared* from the central nervous system in the adult mammal, are found present in perfect condition in the brain of a very high order of animal, and *are not confined, as has previously been supposed, to those of adult reptiles, amphibia, and fishes.*"

If all the data I have submitted are considered collectively, it seems to me that the following conclusion is warranted: *Removal of the hemispheres in an animal does not arrest its power to execute normal bodily movements under external stimulation, because these movements are dependent upon functional structures situated in the base of the brain and in the spinal cord and which the posterior pituitary probably governs.*

Of course, this appears to contradict at once a great mass of experimental and clinical testimony, but the contradiction is only apparent. Removal of the motor areas in the rabbit gives rise to no detectable differences in the movements; the injured animal is similar to an intact one. In the dog, the same procedure, according to Foster, causes "loss or diminution of *voluntary* movement in the corresponding part of the body"; but this is only temporary, and the animal may recover to such a degree that the temporarily paralyzed limb cannot be told from the normal one. Careful examination of the brain after death shows that no regeneration of the lost part had occurred. Even removal of the whole motor area causes no appreciable difference between the movements of the two sides of the body to a casual observer. In the monkey the results have been unequal: "While in some instances recovery of the movement has, in the monkey, as in the dog, after awhile taken place, in other instances the 'paralysis' has appeared to be permanent." . . . "The facts, however, within our knowledge relating to the permanence of the effect are neither numerous nor exact enough to justify at present a definite conclusion," as stated by Foster. "On the other hand, the positive cases, where recovery has taken place, are of more value than the negative ones, since in the latter the recovery may have been hindered by concomitant events of a nature which we may call accidental." I might add that a single case of recovery in the monkey, when the motor area has been completely removed, demonstrates that, generally speaking, the structures are functionally similar in all higher animals, including man, judging from such instances as the crow-bar case, or one reported by Brown-Séquard,¹¹ in which an entire

¹¹ Brown-Séquard: Société de Biologie, 1876.

lobe was destroyed and in which the only symptoms were amaurosis and slight headache. This emphasizes the identity of the cerebral hemispheres as an aggregate of centers which record impressions and are the seat of reason, intelligence, and volition, but it also suggests that the word "motor" is only applicable in its literal sense to the areas in the lower cerebral mechanism: *i.e.*, the intermediary through which the mandates from the hemispheres are executed.

I have previously referred to the misleading information afforded by the use of electrical stimulation. Nowhere in the organism does this seem to be more applicable than to the brain. This feature and the complexity of the processes involved are fully emphasized in the following lines of the late Dr. Foster: "Some writers appear to entertain the conception that in a voluntary movement, such as that of the forelimb, all that takes place is that the 'will' stimulates certain cells in the cortical area, causing the discharge of motor impulses along the pyramidal fibers connected with those cells, and that these motor impulses travel straight down the pyramidal tract to the motor fibers of the appropriate nerves, undergoing possibly some change at the place in the cord where the pyramidal fiber makes junction with the fiber of the anterior root, but deriving their chief, if not their whole, co-ordination from the cortex itself: that is to say, being co-ordinated at their starting-point. That such a view is untenable and that the simplicity of the electrical phenomena is misleading are shown by the following two considerations, among others: On the one hand, as was shown in a previous section, the co-ordination of movements may be carried out apart from the cortex, namely: in the absence of the hemispheres; and we can hardly suppose that there should be two quite distinct systems of co-ordination to carry out the same movement: one employed when volition was the moving cause, and the other when something else led to the movement. On the other hand, the analogy of speech justifies us in concluding that the cortical processes do take advantage of co-ordination effected by the action of other parts of the nervous system."

Referring directly to the general character of the processes involved, Professor Foster says: "Hence, while admitting, as

we must do, that in the intact animal the cortical area and pyramidal tract play their part in carrying out voluntary movements, their action is not of that simple character supposed by the view referred to above. On the contrary, we are driven to regard them rather as links—important links, it is true, but still links—in a complex chain. As we have already urged, we may probably speak of the changes taking place in the pyramidal fibers as being, on the whole, of the nature of efferent impulses; but *we would go beyond the evidence if we concluded that they were identical with the ordinary efferent impulses of motor nerves.*¹² All the features emphasized in these quotations, especially in the last lines, appear to me to isolate the hemispheres from the *source* of motor impulses *per se*, and to confirm what experimental evidence obtained after removal of the hemispheres had suggested: *i.e.*, that the *lower* cerebro-spinal structures constitute the executive intermediary through which the cortical mandates are actively realized. Yet, as is well known, these lower structures, in turn, manifest their activity through the centers imbedded in them; what is there to replace the energy in the form of motor impulses which is erroneously supposed to be awakened by the “will” in “certain cells of the cortical area”?

Professor Foster partially answers this question when he says: “The discussion in a previous section has shown that much of the co-ordination of the body is carried out by the *middle portions of the brain*, and on these the motor area must have its hold as on the spinal mechanisms. The details of the nature of that hold are at present unknown to us.” It would appear from the facts reviewed that what might be termed the *central* brain and the spinal cord constitute an entity—a mechanical entity, perhaps—made up of working centers, beginning with the olfactory bulb and the other nervous structures distributed to the nasal mucous membrane anteriorly, and terminating with the end of the spinal cord: *i.e.*, the neural tract of lower forms. Motility, unconscious co-ordination, and sensation—but only, in the case of the latter, to the extent of *transmitting* sensory impressions to their re-

¹² The italics are my own.

spective perception-centers—would enter within the scope of this central brain.

As to the source of the transmitted energy or impulses,—apart from the sensory connections with underlying structures which the cortex possesses,—the predilection of most writers to ascribe to the cortical areas motor functions but demonstrates the need of such an agency to logically account for the phenomena witnessed. To ascribe to the central brain or its centers *per se* attributes of a similar kind would simply amount to shifting to it a convenient, but unknown, quantity, and a fictitious one besides, in the sense that it supplies nothing to account for something. In the only nervous system that I have so far traced to its origin, that of the suprarenal glands, the conversion of chemical energy into nervous impulses was found to be a functional attribute of the anterior pituitary body. That so extensive a system as that represented by the central brain and cord should likewise need a center such as that represented by the posterior pituitary body for the conversion of some form of energy of external source to satisfy the needs not only of its efferent, but also its afferent, impulses seems clear.

That the middle brain is the source of the motor phenomena witnessed is not only suggested by the fact that normal muscular contractility promptly recurs after removal of the hemispheres, but also by the following experiment by Professor M. Duval: "If a part of the gray substance of the cortex designated as the center of certain movements is cauterized, the same movements are obtained when the electrodes are applied upon the eschar thus produced. . . . This experiment shows," says the author, "that the gray cortical substance is not a necessary experimental condition for the production of localized movements." Indeed, he states that the underlying white substance of certain parts will also cause circumscribed motions in certain groups of muscles, etc.

Can the removal of the cortex of one side be followed by the assumption of compensative functions by the opposite side? After the usual period of paralysis, due to shock, the normal motions promptly recurred, precisely as they had on the other side. To ascertain whether the cortex at all possessed motor

attributes Vulpian passed an electrode through it, that part in contact with the cortex being insulated. The underlying white substance was thus alone stimulated. He found that the latter was far more easily excited than the cortex. It seems clear that in these experiments *the increased excitability was due to the closer proximity of the central brain*. "All the functions of the brain can persist," says Brown-Séquard, "after the complete destruction of an entire lobe."¹³ Experimental and clinical evidence, however, only eliminate motility and co-ordination from the hemispheres. The cortex, as regards cerebral localization, merely loses the "motor" attribute suggested by the term "motor area," and is shown, by its functional relations with the underlying structures, to be a vast sensitive surface, to the "areas" of which the term "sensory" might be more fittingly applied.

The practical bearing of this may be illustrated by an experiment that will recall some of the familiar features of the earlier portions of this work and at the same time point to the central brain as the source of motor phenomena. This experiment, referred to by Professor Foster, is as follows: "It has been observed that in certain stages of the influence of morphine the cortex and the rest of the nervous system are in such a condition that the application of even a momentary stimulus to an area leads not to a simple movement, but to a long-continued tonic contraction of the appropriate muscles." As previously shown, many drugs raise the blood-pressure and thus congest the adrenals and indirectly the brain. Cerebral hyperæmia, we have seen, is the source of the majority of phenomena that follow the ingestion of drugs that are sufficiently active to stimulate the adrenals. The intense headache of quinine and other agents is obviously due to this congestion of the cerebral vessels; muscular contractions, tetany, etc., are also familiar results of suprarenal overactivity; indeed, digitalis, one of the most active suprarenal stimulants, is particularly active in predisposing muscles to contraction and in experimental animals suitably dosed a minimal current without the drug will produce maximum effects—prolonged tetany—with it.

¹³ M. Duval: *Loc. cit.*, p. 115.

In the course of the statements to which I have referred, Foster, after ascribing the temporary paralysis observed after operative interference to a condition "of the nature of shock," remarks: "But, even giving full weight to this consideration, there remains the fact that the cortical area is *associated* with various co-ordinating and other nervous mechanisms belonging to the limbs by such close ties that these are thrown into disorder when it is injured. And, side by side with this, we may put the remarkable fact, previously stated, that during an *abnormal* condition of the cortical area—simulation of the area—instead of producing the appropriate movements confined to the limb may give rise to movements of other parts *culminating in epileptiform convulsions*."¹⁴

If the word "associated" is given its full meaning, limbs and co-ordinating mechanism constituting one class, and the cortical surface the other, *the hemispherical mantle of gray matter being considered solely as a great sensory surface*, the demands of experimental evidence seem to me to be satisfied. What are epileptic convulsions after all but manifestations of excessive *motor* activity? . . . Can the latter be credited to the cerebral cortex, as is now taught in text-books? Obviously not, since experimental evidence proves that the cortex has no motor properties *per se*. But irritation of this sensory surface or an accumulation of physiological toxics, which periodically becomes sufficiently great to so stimulate the vasomotor center as to cause violent hyperæmia, not only of the sensory cortex, but also of its executive mechanism, the middle brain, are the clearly defined causes to which physiological and chemical evidence points. Could the cortex without the middle brain give rise to the same phenomena? That such is not the case is shown by the preservation of all motor functions, including co-ordination, after removal of the hemispheres. Indeed, it is only when the middle brain is removed that the experimental animal thus deprived of its sentient cortex and of its dynamic center practically loses its identity as a living thing. Hence it seems clear that *the motor phenomena caused*

¹⁴ All Italics are my own.

by stimulation of the motor areas of the cortex are manifestations of activity of the central gray matter at the base of the brain, incited therein by sensory impulses from these cortical areas.

What constitutes this lower brain? The co-ordination, so evidently preserved in animals deprived of their hemispheres, points to the cerebellum as a possible member of the group of organs to be considered in this connection. Including this organ, therefore, and beginning with the anterior structures, we would now have: the posterior pituitary body; the infundibulum; the central gray matter, forming "a bed for the development of the nuclei of the cranial nerves"; the tegmental system,—*i.e.*, the reticular formation in the medulla continued to the subthalamie region, and to which belong the red nucleus and other bulbar nuclei. All this forms what Foster so aptly characterizes as "a more or less continuous column of gray matter" connected with the spinal cord by various ties, besides being, as it were, "a continuation of the spinal gray matter." It is as evident that the optic thalami and corpora quadrigemina are also members of the group, since these related organs appear to be necessary for the success of the experiment in which both cerebral hemispheres are removed. Thus, referring to the frog, Foster says: "In this animal it is comparatively easy to remove the cerebral hemispheres, including the parts corresponding to the corpora striata, leaving behind, intact and uninjured, the *optic thalami* with the optic lobes, the representatives of the *corpora quadrigemina*, the small cerebellum, and the bulb. If the animal be carefully fed and attended to, it may be kept alive for a very long time: for more than a year, for instance."

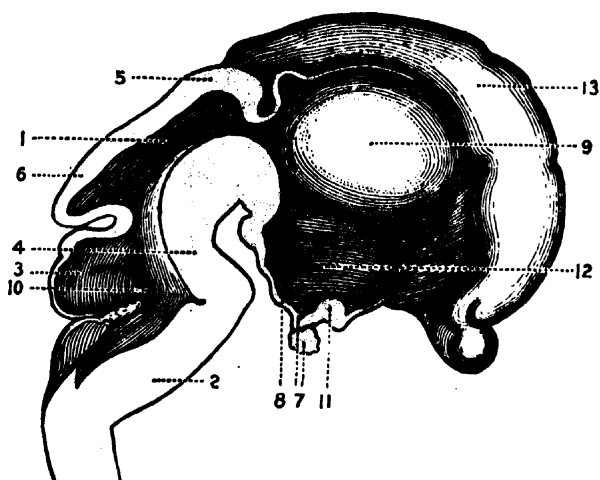
If, with this list before us, we now examine the annexed illustration, originally from His's work, and, therefore, not recently drawn, a rather suggestive coincidence appears, indicating, perhaps, a total independence, in the embryo, of the region containing all the structures enumerated from the vesicle which subsequently develops into the hemisphere of the same side. In mammals the latter is at first insignificant, but it develops very rapidly, soon overlapping the middle structures. The outline of the latter is colored bluish gray. The name of each part is given on the cut: a feature that will

better convey the mutual relations of the various structures included in this system than a verbal description.

Again, the location of the posterior pituitary at the very head of the entire spinal system, as shown in the illustration, adds further testimony to that already submitted to demonstrate the functional relationship between the nervous structures lying in the posterior pituitary, including the floor of the fourth ventricle, and the bulb.

A summary of all these facts, *i.e.*, (1) that the posterior pituitary body has a phylogenetic history which distinctly identifies it as a part of the entire neural tract; (2) that it presents clearly defined histological characteristics of an active neural organ; (3) that these characteristics extend to the infundibulum, the tuber cinereum, the floor and sides of the third ventricle; (4) that these structures are continuous with the reticular substance of the tegmental region, the medulla, and the cord; (5) that the posterior pituitary body has been found to be in direct relation with the olfactory center and the bulbo-spinal axis in all classes of vertebrates; (6) that a current passed between the olfactory and medullar centers may cause heart-inhibition and death; (7) that various nerve-centers are included in the structures with which the pituitary is functionally connected in all vertebrates; (8) that sudden death is caused by a puncture in the region of the vagal bulbar center through interruption of the efferent and afferent impulses through which the cardio-pulmonary system is incited to activity and governed; (9) that electrical excitation of the exposed pituitary body causes an instantaneous rise of the blood-pressure of over 100 mm. Hg.; (10) that removal of the pituitary causes the opposite, *i.e.*, an immediate and great fall of the blood-pressure; (11) that division of the base of the brain across the path of nerves known to originate in the pituitary body prevents the action of drugs, such as antipyrin, which lower the temperature, and also the action of pus and other septic materials which cause fever; and finally (12) that all functions carried on normally after removal of the brain are caused to cease by removal of the pituitary, seems to me to warrant the conclusion that:—

The posterior pituitary body is the chief center of the spi-



MEDIAN AND VERTICAL SECTION OF A TWO AND ONE-HALF MONTHS' EMBRYO. [*His.*]

[Considerably Enlarged.]

1, Aqueduct of Sylvius. 2, Medulla Oblongata. 3, Cerebellum. 4, Pons Varoli. 5, Anterior Tubercula Quadrigemina. 6, Posterior Tubercula Quadrigemina. 7, Infundibulum and Pituitary Bodies. 8, Tuber Cinereum. 9, Optic Thalamus. 10, Fourth Ventricle. 11, Hypoglossal Nerve [Twelfth Pair]. 12, Third Ventricle. 13, Hemisphere Vesicle.

nal system, and, as such the primary source of certain excitomotor impulses now believed to arise in the bulb.

Of course this conception conflicts with the prevailing view that the pituitary body is the source of an internal secretion; but there is ground for the belief that some leading investigators are not convinced of the existence of the latter. Swale Vincent, we have seen, finds it "extremely difficult to imagine how such a structure," referring to the posterior lobe, "can be regarded as a secreting gland." In a very recent paper, E. A. Schäfer,¹⁵ though a partisan of the secretion theory, concedes that "some functions of the organ might be conceived to be carried out through the agency of nerves." Nothing so far published has, in my opinion, raised the secretion theory beyond the level of a plausible assumption. (See also page 173 in the present volume.)

If, however, the posterior pituitary holds the important relation to the nervous system I believe it does, its influence in the pathogenesis of general neuroses must be very great. No disease having so far been associated with the *posterior* lobe, it may prove profitable to seek among the symptoms of typical disease of the *anterior* lobe what signs might be assigned to implication of the posterior, with which it is intimately blended.

Acromegaly, which may be attended by irregularity of the reflexes, paræsthesias, localized pains, vasomotor neuroses, paraplegia, etc., and known to be due solely to lesions of the pituitary, suggests itself as a profitable field of study in this connection.

It is interesting to note, in this connection, that quite a number of exceptionally able clinicians—von Recklinghausen, for instance—have considered acromegaly as a trophic neurosis, the organic disease of the pituitary being deemed secondary. That the various theories adduced also bear upon *nutrition* of the nervous elements is significant as testimony in favor of my view. Indeed, the clinical signs that point to impaired nervous action are numerous, and are present in practically all cases of acromegaly when the anterior lobe has become sufficiently enlarged or functionally disordered to involve the posterior lobe, either directly by pressure, continuity of tissue, etc., or indirectly by overstimulating the adrenals, or, in the later stages, by causing insufficiency of these organs.

¹⁵ Schäfer: Proceedings of the Royal Society of Medicine, May, 1913.

In a previous chapter I have, on good grounds, I believe, ascribed to overactivity of the adrenals the stage of "erethism," and to insufficiency of these glands that of "cachexia." But, if we ask *how* these states are produced by the adrenals, the answer which would not have been available before now seems to be within our reach.

I have previously referred to the vicious circle that obtains in acromegaly. Though primarily located in the anterior pituitary, the lesion probably gives rise to no untoward symptom until well advanced: *i.e.*, until pressure occurs either upon its own structure by the pathological elements or upon the posterior pituitary. Even slight pressure upon the whole organ, as shown by de Cyon,¹⁶ gives rise to marked general symptoms. But if the posterior pituitary is also considered as a factor in the production of the symptomatic phenomena, as a source of nervous energy, we not only have the vascular erethism of suprarenal overactivity, but distinct evidence of *nervous* erethism besides. This is well illustrated by the following *quoted* lines, *i.e.*, Gauthier's definition of the erethic stage of acromegaly as given by Hinsdale¹⁷: "The phenomena of *erethism* which characterizes the *first stage* embraces, first, a painful *hyperæsthesia*, which manifests itself in headaches and rheumatic pains; second, an hypertrophy of the muscular fibers which may give to patients a muscular power greater than usual; third, palpitation of the heart accompanying the hypertrophy of that organ; and, finally, the polyphagia and polyuria which may be considered to be connected with an erethic state of the respective organs." Everything here points to overactivity. But these are only the milder manifestations. Tamburini, for instance, describes a case in which "the mental symptoms, on account of which the patient was sent to the asylum, began to show themselves only a year before her admission. They consisted chiefly in delusions of suspicion accompanied by threats and acts of violence. The patient presented, in a marked degree, the bodily changes characteristic of acromegaly. While in the asylum she was confused, resistive,

¹⁶ De Cyon: *Archives de Physiologie*, July, 1898.

¹⁷ Hinsdale: *Loc. cit.*, p. 30.

and suicidal, and refused her food. . . . Only the anterior lobe was involved, the posterior presenting no change either in volume or structure." This typifies the irritability or stimulation induced by pressure without organic change.

The phenomena produced are of another kind when both organs are involved in the morbid process, as appears to be the case in the following instance reported by Johnston and Monro¹⁸: The patient, a woman, "was taciturn and intellectually obtuse, and her memory was bad. Her utterance was thick and indistinct, as if her tongue were too big for her mouth. Her gait was slow and shuffling; her expression partly melancholic, partly demented. . . . The skin of the face is of a dull-yellowish tint; the mucous surfaces are pale. . . . Hearing is somewhat impaired. Reflexes are diminished. The subject of these notes remained in hospital for about four weeks. She scarcely ever spoke, took no interest in anything, and slept about sixteen hours daily. . . . She was readmitted in September—blind, more deaf, more drowsy, very feeble in muscular power. She could no longer rise without assistance. Control over the sphincters was lost. . . . Paralyzed. For a couple of months before death there was a discharge of clear fluid from the nose. . . . The pituitary body is represented by a large, red mass, almost diffuent—much softer than brain-substance." The entire organ being destroyed, the posterior lobe had obviously followed the fate of its mate.

In a case described by Pirie¹⁹ the history of the nervous symptoms is very clearly defined, though the author was unfortunately unable to obtain an autopsy. "The disease first manifested itself in 1886, when menstruation finally ceased. Pains and paræsthesia of the arms and legs were felt, and the patient noticed that her hands and feet were getting larger and more awkward. . . . Along with the development of physical symptoms a peculiar alteration of mental condition took place. Attacks of narcolepsy overcame her, she became sluggish and irritable, and she suffered much from the *ennui* of life. . . . Breathlessness on the slightest exertion ap-

¹⁸ Johnston and Monro: Glasgow Medical Journal, August, 1898.

¹⁹ Pirie: London Lancet, Oct. 5, 1901.

peared, and ultimately the muscle weariness so gained upon her that she had to take entirely to bed. . . . Sensory disturbances are marked. Shooting pains in combination with paræsthesia, tingling, and numbness are complained of in the arms and legs. Neuralgic pains are felt also in various parts of the body, viz.: the face, chest, back and loins. A remarkable perversion of thermic sensibility is found in the lower limbs and over the front of the abdomen and chest up to about the level of the fourth rib, the patient having no sensation of heat in these regions. . . . Sternberg remarks particularly on the occurrence of pain and paræsthesia as valuable signs for diagnosis in the early stages of the disease; they are probably due, he considers, to changes in the cutaneous nerves."

In a previous chapter I remarked: "Whether the mental symptoms are ascribable to the cerebral hyperæmia or to the impairment of certain functions of the pituitary itself, or to both, it is as yet impossible to say." It now seems evident that *both* organs are involved in the pathogenic process. If the far-reaching meaning of this fact is apprehended, it seems clear that there lies hidden under the whole fabric—of which we only now see the outline—a truth of overwhelming importance to us physicians: *i.e.*, the fact that *it is not alone in acromegaly that the typical signs of impaired function of the posterior pituitary appear, but in other syndromes directly ascribable to the adrenal system: i.e., myxædema, cretinism, exophthalmic goiter, and Addison's disease, which include in their aggregate the majority of organic changes of a morbid kind to which the system is liable, besides nervous phenomena.*

This may be briefly illustrated by further quotations from Dr. Pirie's excellent paper, entirely devoted to the one case. As regards the *muscular system*, the author states that "muscular atrophy is a prominent feature, affecting the thenar, hypothenar, and interossei muscles of the hands, the forearm- and arm-muscles, the calf- and thigh-muscles, and also the glutei," and refers to Duchesneau,²⁰ "who has made a special study of the atrophy of muscles in acromegaly. So marked is it in some cases that it has been mistaken for syringomyelia,

²⁰ Duchesneau: Thèse de Lyon, 1891.

progressive muscular atrophy, or amyotrophic lateral sclerosis; it has also been mistaken for Charcot's cervical pachymeningitis hypertrophica and for erythromelalgia." Referring to the *skin*, Pirie says: "Its chromatogenous functions are disturbed, much as in rheumatoid arthritis. Small freckles are frequent; patches of a yellowish bronzing occur also on the face, the chest, and the insides of the thighs. (Motais describes a bronzing such as occurs in Addison's disease.) Numerous small warts are present. (Mollusca fibrosa are described in many cases and xanthoma-like tumors by Dallemagne.) The patient suffers from a brownish seborrhœa, especially troublesome in the scalp. The hair is thick and coarse and stands straight upward. There is a scanty beard and moustache. Profuse perspirations are constantly complained of. The heart is dilated. There is tachycardia, the heart beating about 98 to the minute. A soft, systolic, basic murmur is heard at times. Palpitations and fainting fits occur very often. Dyspnœa is marked, and asthmatic-like attacks occur, during which the patient has to sit up in bed and fight for her breath." . . . "The *soft parts* are remarkably changed as well as the *bones*. The scalp is much thickened, as is also the skin of the face. . . . In addition to the kyphosis there is a compensatory lumbar lordosis and also a certain degree of scoliosis. The clavicles are enormously hypertrophied. The ribs are thickened and expanded, the costal cartilages feel bony, and there are nodular projections resembling the 'rachitic chaplet' at the junctions of the ribs and their cartilages." . . . "With regard to the *organs of special senses*, the skin of the eyelids is thickened and puffy. The lacrymal glands are hypertrophied. Increased lacrymation occurs at times, and I have noticed a colloid-like secretion between the eyelids." . . . "There is amblyopia, nearly complete in the left eye, and color-vision for blues and yellows is defective. Bitemporal hemianopsia is present. The pupils contract in accommodation and react to light, though very sluggishly in the case of the left eye. With the ophthalmoscope optic atrophy is found." . . . "She suffered much at this time from polydipsia and *glycosuria*, and for over twelve months there was an almost constant dribbling of saliva from the mouth. . . . The

thyroid was greatly enlarged, but under treatment with thyroid substance it diminished much in size." We have seen how dependent the organism is upon the integrity of the suprarenal system when infectious diseases develop.

I can fully agree with Harlow Brooks²¹ when he says: "It is quite natural to expect pronounced abnormalities in the various portions of the nervous system in a disease which exhibits so many neurological symptoms"; and his statement that "examinations of the nerve-tissues have shown quite *extensive* and *general* changes" further sustains my deductions. Evidence of this kind, garnered from all sides long before the feature it serves to support is thought of, appears to me of the strongest kind. I again prefer to use the author's own words, therefore, rather than my own, when he reviews the pathology of the disease, and which seems to me to portray *in parvo* the main landmarks of neurological pathology. I have only omitted those of the author's own estimates that do not bear directly upon my subject and what text was not purely descriptive:—

"Peripheral Nerves.—The trunks of the peripheral nerves are, for the most part, enlarged; this is directly due to an increase in the connective tissue of the endoneurium and perineurium. Often the sheaths of the nerve-trunks also show considerable thickening. This general connective-tissue hyperplasia frequently so encroaches on the nerve-fibers as to destroy them, and degenerated nerve-fibers are quite commonly found some of which may show complete axis-cylinder destruction (Arnold, Comini). These conditions may persist throughout the entire nerve-trunk, extending even into the nerve-roots. (Arnold, Duchesneau.)

"Ganglia.—In the posterior-root ganglia, also, we find the connective-tissue elements greatly increased, so that even macroscopically the ganglia are often considerably enlarged. Microscopically the ganglionic cells are sometimes pressed upon and atrophied (Marie, Marinesco). Arnold reports that he found vacuoles in the nerve-cells. In Cases I and II of the author's, the alterations in the ganglion-cells were slight.

²¹ Harlow Brooks: *Archives of Neurology and Psychopathology*, vol. 1, No. 4, 1898, p. 592.

"It is difficult to determine whether the nerve-cell lesions are secondary, perhaps directly dependent on the connective-tissue hyperplasia about the cells and fibers, or are primarily due to defective nutrition of the ganglion-cell bodies. Perhaps these ganglionic changes are wholly, or in greater part, responsible for the degenerations and atrophies which take place in the muscles of the voluntary system.

"Sympathetic Ganglia.—The changes in the sympathetic ganglia and trunks have been made the subject of special study by several very prominent investigators, among whom are Marie, Marinesco, and Arnold, and have been looked upon by many as factors of an etiological nature. Finding, as we do, such pronounced change in the blood-vessels, it does not seem at all strange that lesions in the sympathetic ganglia should be present; but a view intimating a dependence or relation of the vascular changes to the lesions in the sympathetic system is not in accordance with our own ideas expressed at the close of this paragraph. In general, the changes in the sympathetic ganglia are very similar to those already described in the ganglia and trunks of the cerebro-spinal system. In some cases the size of the ganglia is considerably increased (Arnold, Marie, Marinesco), and, microscopically, the connective-tissue web is thickened and proliferating. The ganglion-cells are often reported as exhibiting evidences of degeneration." . . . "Arnold has found vacuolization; not infrequently considerable deposits of pigment are seen within the cytoplasm. But, as in Case II, the ganglion-cells may be normal; the Nissl bodies are present in normal arrangement, volume, and shape, and show no deviations in their staining reactions; and the pigmentary deposit is not abnormally abundant. The sympathetic ganglia in the case reported by Gauthier were also normal. It is advisable, at this point, to call attention to the fact that the interstitial hyperplasia is by no means a lesion characteristic of the sympathetic system, but is simply an extension of the general process so often alluded to. The growth of connective tissue in the sympathetic may depend in part on lesions in the walls of the vessels; or both may be referable to the common factor of deranged nutrition.

"Cord and Medulla.—The pathological findings in both

the cord and medulla differ greatly. Virchow, and also Fritsche and Klebs, have reported hypertrophy of the medulla. The spinal cord was enlarged in the case reported by Linsmayer. Many observers have reported various degenerations in the cord. Baruch's case was associated with symptoms of syringomyelia; Debierre gives a case with diseased posterior columns, while Arnold, Dallemagne, and Tamburini have found at autopsy irregular degenerated areas in the cord, affecting, however, no special place with any degree of constancy."

That the trophic changes in the nerve-tissues explain several of the neurological and myological symptoms in acromegaly is obvious, but these occur in *advanced* cases, *i.e.*, when such morbid changes have had time to occur. The signs which point to the posterior lobe as the seat of an important center—in keeping with physiological data enumerated on page 510—occur during the *early* or erethic stage, *viz.*, the painful hyperæsthesias in the extremities, the tingling, numbness, the vasomotor neuroses and the palpitation. Their presence is explained by the marked rise of blood-pressure produced by irritation of the pituitary body proper, observed by Cyon, and confirmed by Masay, and by the long-recognized identity of the posterior pituitary as the *neural lobe, its histology and nervous connections*.

Pending additional evidence in this direction the nature of the process through which the pituitary influences the nervous system requires study.

THE HISTOLOGY AND PHYSIOLOGICAL CHEMISTRY OF THE NEURON.

We are first brought to inquire into the relationship between the modern conception of the structural composition of the cerebro-spinal axis and the views I have submitted. Granted, therefore, that the posterior pituitary body is the seat of a process through which chemical energy is converted into nervous energy, and that this constitutes the nervous impulses which the cerebro-spinal axis transmits to the various organs, how do the nerve-elements utilize this energy when functionally active?

I refer, of course, to Waldeyer's neuron as the morphological unit of the cerebro-spinal axis, and the processes of

which are not in contact, but sufficiently close, one to the other, as to make it possible, when required, for a nerve-impulse to cross the interval between them. These facts have been satisfactorily established by modern methods, especially through the labors of Golgi and Ramón y Cajal. But the manner in which the gap between the processes is closed—*i.e.*, how the impulse passes from the terminal brush of the axon of one nervous element to the dendrites of the next—is still to be determined. It has been suggested, however, that the processes behave, in a limited manner, as do the pseudopodia of the amœba, and that by a slight extension the interval between the processes is closed. When the processes are not in contact they are said to be in a state of “retraction.” Much as such a function would facilitate and shorten our analytical work could incontrovertible experimental facts be adduced to sustain it, we are brought, by a review of the literature of the subject, to recognize that such facts are not available. Indeed, the majority of physiologists and neuro-histologists now consider the question of “amœboid movements of the neuron” in the light of a working hypothesis.

There is one feature of the investigations in this direction which may serve to throw more light upon the whole question if one of the more prominent deductions submitted by me in the present work is taken into consideration: *i.e.*, the fact that certain drugs cause overactivity or insufficiency of the adrenals.

Much of the physiological work done in connection with the neuron includes the administration of various toxics,—strychnine, chloroform, morphine, etc.,—and amœboid movements or other active manifestations of the protoplasmic processes are thus ascribed to the action of the drugs upon the neurons *per se*, whereas, in the light of my views, the changes of form witnessed should be ascribed to increased or reduced blood-supply when toxic doses are given. To illustrate my meaning I will give in outline an experiment which represents one of the key-stones of the entire theory, that of Demoor. Before doing this, however, it may, perhaps, be well to state that I will consider the terms “neuron” as applying to the complete nerve-cell, including processes; “neuraxon”

to the (usually) single and long process which extends along the center of the nerve-fiber, and is then called "axis-cylinder; *"dendrites"* to the cell's many processes—some of which end in many branches or tufts—other than the neuraxon. With Foster and Sherrington we will consider that neuraxons carry impulses *away* from the cell, while dendrites transmit impulses *into* the cell. Two other prominent morphological features are the "*gemmules*"—minute projections all along the dendrites—and their terminal twigs, which recall those on the stems of the moss-rose, and the *varicose*, or irregular, swellings that may be observed in the course of the dendrites or their terminal twigs.

The experiment of Demoor was briefly as follows: He *killed* a dog by injections of morphine; a second dog was given morphine for some time, then killed by cutting the medulla; a third was trephined. The next day a piece of the left hemisphere of the latter dog was removed; the animal being then morphinized, another piece—but of the right hemisphere this time—was removed. Portions of the hemispheres of the two killed dogs having also been removed, all specimens were treated in precisely the same manner. The cellular changes were found to be similar in all specimens taken from the morphinized animals: their gemmules had disappeared. Alone of the series the piece removed before morphine had been given was covered with regularly distributed gemmules. Now the fact I wish to emphasize is this: while this experiment is thought by its author to show that the retraction of the gemmules constitutes the inactive state, as induced by morphine through the *local* action this drug is now thought to have upon nerve-cells, the retraction of the gemmules is due to general vasoconstriction of all arterioles, *including those of the adrenals*, by a direct action of the morphine upon the sympathetic center. (See page 1272.) We thus have, instead of a purely local effect, an example of the general physiological process through which the neuron passes from the active to the passive state, the circulation of oxidizing substance in the neuron being thus inhibited.

Again, the same structures treated by different methods have been found to yield different results. Thus, H. H. Baw-

den²² found that "all material treated according to the slow method of Golgi shows, as a rule, an almost absolute freedom from varicosities; varicose cells occasionally occur." The mixed method and the rapid were found to yield practically the same results when the dendrites had taken the stain: the gemmules were almost invariably present and regular. In some sections almost every dendrite was varicose; in others hardly any. All these results were similar whether normal or "toxic" material was used, and the author concludes that "it is impossible for an unprejudiced observer to differentiate or distinguish between the two kinds of material." Lugaro,²³ who has upheld the retraction theory, also reached the conclusion that "imperfect fixation is very largely, though not entirely, responsible for the formation of varicosities and the disappearance of gemmules." Weil and Frank summarize what a review of the literature of the subject shows, when they say: "The findings have been in almost every case positive, although there are occasionally records of negative results and even contradictions,—as, for example, between the investigations of Demoor and of Soukhanoff on the effects of chloroform. . . . Retraction of the gemmule and coincident swelling of the dendrites form the essential features of every description."

Judging from the foregoing estimates as to the effects of stains upon dendrites, these phenomena are to be considered as artifacts: *i.e.*, as artificially produced changes. Under these conditions, it is clear that the latter should appear, irrespective of the condition of the animal at the time of its death: *i.e.*, whether under the influence of toxics as stated, fatigue, etc.

That prevailing views in this connection are erroneous is my firm belief after a critical analysis of available experimental evidence. Particularly instructive and valuable in this connection are the experiments of H. H. Goddard,²⁴ which consisted "in cutting through the entire head of the animal at a single blow with a very thin sharp knife, the parts of the head falling instantly into large dishes of Cox's solution warmed

²² H. H. Bawden: *Journal of Comparative Neurology*, May, 1900.

²³ Lugaro: *Rivista di patol. nerv. e ment.*, vol. III, 1898.

²⁴ H. H. Goddard: *Jour. of Compar. Neurol.*, Nov., 1898.

to 39° C. In his first experiment, puppies about seven weeks old, sisters from the same litter, were used, the one while somewhat tired, the other after having slept. A careful count of the pyramidal cells of the cortex of the somewhat fatigued puppy gave a proportion of 31.1 per cent. of cells showing varicosity, while cells from the same region of the puppy killed after sleeping was 8.5 per cent. In the former animal 15.9 per cent. of the cells showed much varicosity; in the latter only 0.8 per cent. showed a similar state. In the second experiment the first of two sisters was killed on waking in the morning; the second at night when tired and very sleepy. While it "was difficult to find a single varicosity on the dendrites of the morning puppy, for long distances in the cortex of the evening puppy" it was difficult to find a cell "whose processes" were "not more or less varicose." It is evident that in these instances at least the stain was not alone the source of varicosities, since it was only in the tired puppies that the varicosities were very marked, while in the thoroughly rested animal practically none could be found.

Judging from these experiments, varicosity of the dendrites coincides with a fatigued condition. This corresponds exactly with the experiment of Demoor, previously described, since retraction of the gemmules is accompanied by varicosity; so that fatigue and a large dose of morphine must have produced similar results.

If the staining process alone caused the formation of varicosities in Demoor's experiments,—the same method having been used for all specimens,—how is it that one of the latter showed gemmules (which means absence of varicosities), and that this solitary specimen is precisely from the only animal which had not received morphine? Berkley²⁵ found that poisoning with alcohol "in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum" very similar in character to the pathological lesions produced by other more virulent soluble poisons. The terminal twigs of the dendrites were also found to have become varicose

²⁵ Berkley: *Brain*, Winter, 1895; and *Johns Hopkins Hospital Reports*, vol. vi, 1897.

or beaded, the gemmules being very scarce or absent. Here, again, is a condition which, as does fatigue, morphine, and, we may add, chloroform, chloral hydrate, and other toxics used by Demoor and others with similar results, all tend in the one direction: *i.e.*, to morbidly reduce functional activity. This is a well-known characteristic of the bromides. In a study of the cortical cells under the influence of poisonous doses of potassium bromide, H. K. Wright²⁰ says: "If the primal ascending dendron is followed to its visible termination, several ampullous or varicose swellings of varying size are met with," . . . "on the basal processes also varicosities are to be seen; but they are small and, like those of the ascending protoplasmic process, are sharp in outline, and shorn of the lateral projections which obtain on the unaltered part of the extensions. One may be seen on each secondary branch, and ranges in size from a small and *scarcely recognizable* to a *readily obvious* swelling. None of them, however, reach the dimensions of the apical projection and its branches."

If the method of staining is the cause of all this, we are brought to the conclusion that it must be selective as to the parts of the dendrite it affects, and that only functionally-impaired cells are so affected by the stain as to show varicosities. Even then staining methods would furnish precious indications. But it seems clear to me that, while the newer chrome-silver methods still furnish imperfect pictures of the morbid alterations of the neuron, they cannot with justice be said to either cause or prevent the formation or disappearance of gemmules and varicosities; in other words, that they are not artifacts of the Golgi method. The marked tendency of the swellings to locate at the apices, and the gradual reduction of the varices as the cell-body is approached recall, on the other hand, a well-known pathological principle: *i.e.*, that the morbid effects of impaired general nutrition are first felt by terminal structures.

And the painstaking experiments of Weil and Frank do not appear to me in the least to prove their conclusions that "the varicosities must be regarded as artifacts" and that "they

²⁰ H. K. Wright: *Brain*, Summer, 1898.

depend for their presence and their amount on the form and method made use of." Demoor employed the same method in each of his *comparative* experiments and his results were not similar, the non-morphinized specimen alone differing from all others. Hubbard used the identical method in both his *comparative* experiments, and likewise obtained results which distinctly showed a marked difference between the rested and fatigued animals. In these and other experiments referred to, the pathogenic agency, including fatigue, was allowed sufficient time to produce alterations in the cortical cells, if *nutrition* has anything to do with the process.

In Weil and Frank's experiments the animals were overwhelmed by the quantity of toxic administered, and death occurred, viewed from my standpoint, by arrest of the adreno-cardiac functions, long before any *marked* action upon the cells could possibly have occurred. The doses of morphine administered were 0.38 and 0.41 gramme (6 and 7 grains), respectively, with death in 15 minutes; of strychnine nitrate, 0.018 gramme ($\frac{1}{3}$ grain), death in 20 minutes; of hypertoxic urine, 125 to 150 cubic centimeters (4 to 5 ounces), death in 15 to 25 minutes. That these are overwhelming doses in rabbits is evident. One animal was killed with serum (30 cubic centimeters—1 ounce) in 5 minutes; others with chloroform inhalations in 10 minutes; one by tracheal clamping in 8 minutes. The rest, six animals, were destroyed instantly by instrumental procedures. In none of these animals was there any distinction established as to whether they had been sleeping, eating, or romping, etc. That some were old and others young in the series of nineteen is probable; as is well known, erethism, especially in such delicate structures, is greatly influenced by age, and a few months in the rabbit represent as many decades in man. The weight of each animal was not recorded in order to establish the relative action of a given dose of the toxic used per pound of animal, though, of course, in the experiments, the large doses used precluded any usefulness on this score.

Finally, the authors themselves will surely admit that "no varicosities," "varicosities," "slightly varicose," and "very slightly varicose," the method of notation utilized by them,

conveys but little exact information. And still, even this sustains a deduction opposite to theirs. Indeed, the short period of time that elapsed between the injection of the toxics in the animals killed in this manner—represented by 108 blocks of slides—must have sufficed to initiate retraction of the gemmules and the formation of varicosities, since only 10.2 per cent. of these blocks show no varicosities. When, on the other hand, the proportion of animals killed instantly by instrumental procedures—93 blocks of slides—is analyzed, over two and a half times as many, *i.e.*, 28 per cent., are found to show *no* varicosities.

But a fair question suggests itself in this connection: Why do the remaining 72 per cent. show any varicosities? Only 14 per cent. of the blocks from the instantly killed animals are recorded as “varicose,” the remaining 58 per cent. being entered as “slightly” or “very slightly” varicose. In their explanation of the scope given these terms, the first means “at least some varicosities” and the second as “only very few varicosities.” Now, the authors state that “in the first nine cases here recorded the brains were placed in fixing fluids within three to five minutes.” Nothing is said of the rest; so that we may infer that the ten other brains were immersed after longer intervals. We have previously seen, when the conversion of myosinogen into myosin was studied, that oxidation processes continued even after death: *i.e.*, until all the oxygen had been utilized. That this must be the case with the brain, which contains one-fifth of the blood of the whole body, and that products of metabolism, especially CO_2 , should form in the entire encephalon is evident. It normally follows that we have in this factor a potent cause for the retraction of gemmules and the formation of varicosities.

Indeed, the contrast between the results reached speaks for itself when compared to those of Goddard, who resorted to procedures in which the exact condition at the instant of death were preserved, “the parts of the head falling *instantly* into large culture dishes warmed to 39°C .” Even continuation of the normal brain temperature was insured. And what were Goddard’s results? “It was difficult to find a single varicosity on the dendrites of the morning puppy,”—*i.e.*, the thor-

oughly *rested* animal; while in the thoroughly *tired* one "for long distances in the cortex . . . it is difficult to find a cell whose processes are not more or less varicose." That fatigue is the result of an accumulation of products of metabolism and especially CO_2 is generally recognized.

Goddard's procedure appears to me to represent as nearly perfect a one as available staining methods (Cox's and the rapid method show considerable parallelism in Weil and Frank's report, while the mixed and slow methods appear unreliable and contradictory) will allow; *his results, in my opinion, portray the actual changes that are produced in the neuron under the influence of certain poisons and during sleep: i.e., when the blood-supply of the brain is reduced.*²⁷ (See plate p. 1264).

Weil and Frank state that they "are able fully to corroborate the statement of Cajal that normal and toxic material cannot be differentiated by the number of varicosities or of gemmules." The care with which such experiments must be conducted, apart from the method of staining adopted; the need of immediate immersion, and other details to which we have referred, invalidate any opinion that the distinguished Spanish histologist may have expressed on this score, unless he can show that his experimental *physiological* procedures were as perfect as his staining work must have been. Indeed, I must express the belief that the greater part of the physio-histological work done so far in this connection is valueless owing to the absence of the precautions to which I refer.

Again, Ramón y Cajal's conclusions that "the nerve-cells do not move, but on the other hand, that the neuroglia-cells do move" (which underlies his view as to the gemmules and varicosities showing no difference when normal or "toxic"), has been shown by Dercum to embody its own refutation. "Cajal," says the latter author, "points out the fact that the processes of the neuroglia-cells have numerous short arbores-

²⁷ We wish to particularly emphasize the fact that we are in no way criticizing adversely the work of Drs. Weil and Frank. We have nothing but praise to express for these investigators. Much of the searching inquiry to which we are submitting their paper includes the use of features introduced for the first time in the present work, and obviously unknown to them. Indeed, if our views eventually prove to be sound, we will owe much to the counter-evidence Drs. Weil and Frank—and, we may add, Dr. H. Heath Bawden—have published.—S.

cent and plumed collaterals, and he states that in these cells two different phases can be observed: first, a stage of contraction,—that is, a stage in which the cell-processes become shortened; and, secondly, a stage in which the cell is relaxed,—that is, a stage in which the processes of the neuroglia-cells are elongated. He maintains that the processes of the neuroglia-cells represent an insulating and non-conducting material, and that during the stage of relaxation these processes penetrate between the arborizations of the nerve-cells and their protoplasmic processes, and so make difficult or impossible the passage of the nerve-currents; on the other hand, in the stage of contraction the processes of the neuroglia-cells are retracted, and they no longer separate the processes of the nerve-cells, and the latter are thus *permitted to come into contact*.²⁸ Evidently Ramón y Cajal admits the very thing against which he contends, for if the nerve-cell processes are at one time not in contact and at another are in contact, they must certainly move, and the question before us is self-admitted. It matters not whether the processes of the nerve-cells move little or much, but that they move at all is the question at issue, and this Ramón y Cajal admits, though he makes the movement a purely passive one."²⁹ To me it appears clear that, since Ramón y Cajal held the nerve-cell to be a passive structure, requiring an independent connecting-link to close the circuit with the adjoining cell, he must have denied both the gemmules and the varicosities any physiological importance. His opinion, therefore, that normal material cannot be differentiated from toxic material, when applied to the retraction of gemmules and the formation of varicosities, cannot be said to rest upon solid premises, and, for the time being at least, to in no wise affect the question.

In a comprehensive review of the anatomy and physiology of the nervous system, L. F. Barker³⁰ makes the following remarks: "The physiologist of the present day sees in the func-

²⁸ We will see farther on that Cajal's observation as to the relaxation and contraction of neuroglia-cell processes is valuable in that it proves that the tips of the gemmules do not transmit nervous energy.—S.

²⁹ Dercum: *University Medical Magazine*, April, 1897.

³⁰ L. F. Barker: *New York Medical Journal*, May 15 *et seq.*, 1897-98.

tions of the nervous system, even in those which are most complicated, only certain manifestations of energy. Moreover, he believes that in neurons, as in all other cells of the body and as in the world generally, the law of the conservation of energy during transformation holds, and consequently regards the phenomena of irritability, as exhibited by a neuron or by groups of neurons, as the kinetic representative of the potential forces of the cells and their foodstuffs. The metabolic activities and the vital manifestations of the cell are concomitant processes—another example of the inseparable connection which exists between what we term matter and energy. There has been in many quarters a certain amount of hesitancy in accepting the view that the capacities of the nervous system, particularly those of the brain, are dependent directly upon the chemical and physical alterations which are continually going on within its constituents: a hesitancy which, though it has in the past proved a serious obstacle to progress, is happily now fast disappearing. For the plant, all the evidence goes to prove that under the influence of sunlight and heat marked chemical and physical changes take place within it which we recognize in its vital processes. In the animal—be it granivorous, carnivorous, or, like man, omnivorous—it is the chemical energy introduced as food which represents, in the main, the source of the energy of the organism. . . . *The physiologists have been struggling for fifty years or more to gain an insight into the nature of what they call nerve-impulses*, by which is to be understood the occurrences inside axons: for example, at the time when we have good reason to believe that they are functionally extraordinarily active. Their efforts have supplied us with a multitude of data, physical and chemical, interesting enough, no doubt, but which can serve as only the barest prolegomena to an explanation of the essence of the occurrences. If we are so badly informed concerning these elementary and fundamental phenomena we may very well be content to be modest for some time to come in our claims as regards a physiological psychology. It is by no means impossible that in the nervous system forms of energy are concerned which do not exist outside the animal body and which yet remain to be recognized and studied. . . .

Truly, to find out the properties of a single neuron would be a task appalling enough; but, when we remember that of the millions of neurons in one individual perhaps no two are just alike, the quest would seem hopeless. But instead of burying ourselves in pessimistic reflections, or being discouraged by what is at present unattainable, by what may perhaps forever remain to us unknowable, we may profitably turn to the consideration of some of the points which lie more within our ken. One point, self-evident enough when one's attention is directed to it, but which often appears to have been overlooked in connection with the neurons, is the unremitting character of their activity. With a metabolism as complicated as that occurring within the nerve-units it is inconceivable that there can be any period in which alterations in chemical structure, and consequently energy transformation, are not going on. From moment to moment, throughout all the hours of the day and night, analytical and synthetic processes are taking place, associated with the alterations in physical forces which necessarily accompany these changes. In common with everything that lives, the neurons know no absolute repose. As I have said, in speaking of their metabolism, periods of extravagant activity may alternate with periods of more economic change, but total rest is inconsonant with continuance of existence. We are forced to believe that what we ordinarily speak of as the passage of a nerve-impulse represents, as it were, *a stormy process in the nerve-fiber*, and that just as absence of a storm does not mean absence of weather, there are in all probability minor alterations—currents, if you will—passing to or fro or *passing to and fro in a given nerve-fiber in the intervals* between the more violent excitations."

The words that I have italicized will doubtless recall some of the more prominent features previously emphasized in respect to the relative nervous processes involved in the functions of the various organs reviewed. I have termed "passive" that form of energy continuously transmitted to tissues and vessel-walls. A quiet and steady flow of blood into the cellular structures, sustained by the tonic contraction of the arteries, and a stream of nervous impulses to the tissues coinciding in rhythm, perhaps, with that sent to the vessels,

suffice to insure nutrition and to hold the structures thus supplied ready for active work. What is the source of *this* energy?

If the posterior pituitary reinforces the flux of impulses when functional activity is demanded, passive energy would seem to require another source, and as the lower, or middle, brain and the cord are included in the "sphere of influence" of this organ, the hemispheres are the only parts of the encephalon that can supply the need. But they do not. Removal of the hemispheres, we have seen, does not impair muscular activity; a frog can jump, a pigeon can fly, etc., and, after a short period of shock-paralysis immediately after the operations, movements return—evidence that their nutritional metabolism, incited and regulated by nervous impulses, continues. Evidently, therefore, the hemispheres have nothing to do with the process; they are solely the seat of the "mind," and constitute an organ among the rest, itself supplied with vasomotor nerves (Obersteiner, Gulland, Huber, Hürthle, Cavazzani, François-Franck, *et al.*), and probably with its own nutritional nerve-system. We are, therefore, brought back to the posterior pituitary as the only organ capable of satisfying the needs of the situation: *i.e.*, as the only source of passive energy.

This suggests that metabolism may suffice, through the agency of the blood's oxidizing substance, to sustain physiological activity during the intervals between "stormy processes of the nerve-fiber"; but this is promptly shown to be a wrong interpretation when the effects of section below the medulla are recalled. As all the arteries of the organism are immediately relaxed, a continuous stream of impulses must have served to hold the vessels in tonic contraction: evidence that passive nervous energy is a factor to be reckoned with. Thus, the fact that all co-ordinated muscular movements continue after removal of the hemispheres relegates to the lower brain the function of supplying active energy—and, obviously, passive energy likewise, the need of the latter being shown by division of the medulla. Indeed, *passive* energy may well be described as passing to and fro in a given nerve-fiber in the intervals between the more violent excitations, while *active* energy can as fittingly be likened to "a stormy process in the

nerve-fiber": both ascribable, it now seems likely, to the one organ, the posterior pituitary body.

To establish the functions of the posterior pituitary within its proper physiological limits, however, it is necessary to ascertain how nervous elements in general and neurons in particular are nourished, since it is upon the degree of perfection with which the nutritive processes are carried on by the blood that the functional integrity of these structures depends.

The fact that a *general* nutritional process prevails, of which the adrenal system is the primary motive agency, I have shown; but it finds further support in the following statements of Professor Barker's—which, of course, but emphasize a generally known fact—that, "in the absence of substances in the body derived from the thyroid gland, the nervous system undergoes very important and serious metabolic modifications, evidenced by the remarkable nervous and mental phenomena with which all are now familiar. On restoring these substances to the body by the administration of a thyroid extract the symptoms may sometimes be made to disappear. It is likely, however, that the neurons find their staple foods in the main nutritive constituents of the blood as derived from the food digested in the stomach and intestines and purified by the lymph-glands and liver."

I have, I believe, satisfactorily shown that the thyroid secretion incidentally sustains the activity of the anterior pituitary body, and therefore of the entire adrenal system, by pouring its secretion into the blood. The functions of the digestive organs we have also reviewed. Among the latter, however, are two upon which I laid considerable stress,—*i.e.*, the spleen and pancreas,—and I called attention to the great importance of trypsin—the splenopancreatic ferment—in the conversion of albuminoid substances, and especially of their toxic derivatives, into benign products. These albuminoid substances, we have seen, then pass through the liver, and, after traversing the cardiopulmonary circuit are distributed broadcast throughout the organism. There is a feature which I kept in abeyance, however,—though a well-known one,—since at the time its true weight would not have asserted itself: *i.e.*, the fact that *albuminoids include nucleins derived from the animal and vegetable*

cells ingested with food, which nucleins contain at least 3 per cent. of phosphorus. We can now realize how great is the physiological rôle of the pancreas and of the spleen in the organism.

Indeed, the functions of these two organs may be said to constitute one of the pillars upon which the vital functions rest. As a constituent of calcium phosphate, phosphorus is found in the bones, teeth, cartilage, and other tissues; in the blood, milk, etc., in quantities which bespeak of its functional prominence, since calcium phosphate is represented by nearly six *pounds* among the organism's constituents. Sodium phosphate—which gives the blood, lymph, and other body-fluids their alkalinity and fluidity, and the potassium and magnesium phosphates, which fulfill much the same rôle, obviously find in phosphorus their main dynamic attributes. But it is when we reach the nervous system that the functional worth of this element reaches its highest mark.

How are nervous structures—neurons, axis-cylinders, sheaths, etc.—adequately supplied with blood-plasma, their oxidizing substance, their phosphorus, etc.?

THE PHYSIOLOGICAL CHEMISTRY OF NERVES.—The functions of myelin, or white substance of Schwann—a jelly-like homogeneous and transparent material which surrounds the axis-cylinder of nerves, and is only separated from it by a thin protoplasmic film—may be said to be unknown. It is a fatty substance, blackened by osmic acid, and which, after death, coagulates and becomes opaque, loses its homogeneity, etc. Myelin is now universally considered as a protective coat: a function which the overlying neurilemma already fulfills. Is myelin fatty in the true sense of the word? Examined chemically in quantities, a very large proportion of dried nerve-substance—about one-half, according to some observers—consists of a peculiar body: *cholesterin*. This body is not a fat, but an alcohol; like glycerin, however, which is also an alcohol, it forms compounds with fatty acids. "Though we do not know definitely the chemical condition in which cholesterin exists during life in the medulla," says Professor Foster, "it is more than probable that it exists in some combination with some of the really fatty bodies also present in

the medulla, and not in a free isolated state." . . . "Besides cholesterin, 'white' nervous matter contains a less, but still considerable, quantity of complex fat whose nature is disputed. According to some authorities rather less than half this complex fat consists of a peculiar body, *lecithin*, which we have already seen to be present also in blood-corpuscles and in muscle. Lecithin contains the radical of stearic acid (or of oleic, or of palmitic acid), associated, not—as in ordinary fats—with simple glycerin, but with the more complex glycerin-phosphoric acid, and further combined with a nitrogenous body, *neurin*, an ammonia compound of some considerable complexity: it is therefore of remarkable nature, since, though a fat, it contains both nitrogen and phosphorus." Cholesterin ($C_{26}H_{44}O$), lecithin ($C_{44}H_{90}NPO_9$), and neurin ($C_5H_{15}NO_2$), as shown by the formulae, are all oxygen-containing bodies. May this supposed coating and insulating material, myelin, not be to the nerve what myosinogen is to muscle?

Cholesterin, we have seen, is associated with hepatic functions. "It is singular," says Professor Foster, "that, besides being present in such large quantities in nervous tissue, and to a small extent in other tissues and in blood, cholesterin is a normal constituent of bile." I have previously referred to the fact that this alcohol, the only one which occurs in the body in a free state, combines with glycocholic acid in the formation of bile, and is thus eliminated by the liver. This view sustains that of Austin Flint, who looked upon cholesterin as an excrementitious product derived from the nervous system: *i.e.*, the result of nerve-metabolism. Cholesterin is present in abundance in the white substance of the cerebro-spinal axis, as well as in the myelin, or white substance of Schwann, in nerves. We have seen, however, that the elimination of excrementitious products by the liver is carried out by the combination of various agencies: mainly glycocholic and taurocholic acids derived from cholic acid through an oxidation process in which the oxidizing substance plays the predominating rôle. That an oxidation process also occurs in a nerve during functional activity is suggested by the following lines of Mathias Duval: "Direct experimentation has shown that the functioning nerve is the seat of *increased combustion*; this

is accompanied by the liberation of heat, the presence of which Schiff has demonstrated even up to the nerve-centers, under the influence of fear, of excitation of the senses, of any cause—in a word—which produces cerebral activity.”

Lecithin—“a conspicuous component of the brain, nerves, yolk of egg, semen, pus, white blood-corpuscles, and the electrical organs of the ray”—suggests its identity as at least one of the sources of energy we are seeking by the fact that if merely allowed to stand at the ordinary temperature its solutions acquire an acid reaction and are decomposed. In the intestines it sometimes breaks up into its constituents: fatty acids, glycerin, phosphoric acid, and *cholin* (Howell). Neurin is, in reality, cholin, and therefore a decomposition product of lecithin. As previously stated, Tappeiner³¹ obtained fatty acids as a result of cholic-acid oxidation. These facts, of course, are only cited as mere landmarks to indicate that we are dealing with oxidizable bodies. As far as the nerves themselves are concerned, therefore, it seems probable that we have in lecithin an agency capable, by the character of its molecule,—*i.e.*, carbohydrates, phosphorus, etc.,—of acting as a potent source of working energy when brought into contact with the oxidizing substance; and in cholesterin the main waste-product of nerve-catabolism.

Admitting, then, that we have in the lecithin of myelin a body capable of acting as a source of energy in a way similar to myosinogen in muscle, how does the oxidizing substance of the blood-plasma reach it? The nodes of Ranvier and the nearilemma that covers them allow silver stains to reach the axis-cylinder, but the myelin itself does not permit of this. This suggests that the nodes themselves—*i.e.*, the rings forming them—may allow the blood-plasma to filter through them, thus bringing the oxidizing substance in immediate contact with the axis-cylinder. The finer anatomy of nerves indicates that such may be the case. Indeed, the nodes referred to occur at regular intervals, and separate the nerve, as is well known, into as many segments, which recall, in a measure, the muscle-fiber and the liver-cell or, at least, features characteristic of both these structures. If the blood-plasma can penetrate the

³¹ Tappeiner: *Zeitschrift für Biologie*, Bd. xii, S. 60, 1876.

nodes of Ranvier as do stains, there only lies between it and the axis-cylinder an extremely delicate layer of protoplasm,—Mauthner's sheath,—which in no way would impede the entrance of the fluid into the axis-cylinder itself.

The term "cylinder" suggests the tubular shape of the latter: in accordance with Remak's view that it consists of a delicate, longitudinally striated tube, filled with an albuminous liquid. The prevailing view, however, is that of M. Schultz, who considers the axis-cylinder as made up of fibrils united by an intervening unknown substance. This seems to me to vividly recall the arrangement of muscular fibers as regards their relation with the blood-plasma: *i.e.*, minute fibers into which the plasma may freely enter. Again, we must not lose sight of the fact, in this connection, that the axis-cylinder is nothing but the elongated axon of a neuron, and that the fibrillæ now referred to, therefore, represent the intimate structure of a neuron's axon. Now, as Schäfer holds that these fibrillæ are extremely fine tubes filled with fluid, and as the character of this fluid is not known, I have good reason to believe that *they are channels for the blood-plasma: i.e., for the oxidizing substance.*

But there is another feature which points to the axis-cylinder as a channel for the oxidizing substance: *i.e.*, the fact that the so-called "medullary sheath"—*i.e.*, the myelin itself—contains a supposed "supporting frame-work." The striae representing them were at first termed "clefts" or "incisures" by Schmidt, Lautermann, and others, but Ranvier considered them as protoplasmic septa which subdivide each internodular segment of the nerve into several conico-cylindrical chambers. W. H. Wynn,³² who gives an excellent review of this subject and the results of personal researches, refers to those of Rezzonico³³ and Golgi,³⁴ who "from the examination of fibers treated by a mixture of bichromate of potash and osmic acid, and afterward by nitrate of silver, find that each cleft is occupied by what appears to be a thread of darkly-stained substance passing *spirally around the fiber.* They consider," he

³² W. H. Wynn: *Journal of Anat. and Physiol.*, April, 1900.

³³ Rezzonico: *Archivio per le Sci. med.*, Torino, vol. iv, 1880; and *Gazzetta med. ital. lomb.*, Milano, vol. i, 1879.

³⁴ Golgi: *Arch. per le Sci. med.*, Torino, vol. iv, 1880.

adds, "that the supporting frame-work of the sheath consists of a *chain of funnels* surrounding the axis-cylinder, each funnel being formed by a spiral thread." Tizzoni³⁵ "believes that there is but one net-work closely investing the axis-cylinder, and that it is *in connection with* the slits of Lautermann." McCarthy is stated to have shown that, "after a nerve has been hardened with picric acid and ammonium chromate, the medullary sheath contains minute, rod-like structures, which pass rapidly between the axis-cylinder and the primitive sheath so as to give the cross-section of a fiber the appearance of a wheel. The rods stain with carmine and hamatoxylin, which do not stain the myelin. It is not possible to isolate the rods as separate elements, for they are not distinct from one another, but united." Finally he refers to the fact that Lautermann, von Stilling, Roudanowski, and McCarthy all believe that there is "a system of *hollow canals* in the sheath of the axis-cylinder," and himself reaches the conclusion that the cones they form are protoplasmic, and not composed of neuro-keratin, as is usually held. He divides "each cone into six segments placed at regular distances apart and converging from the primitive sheath to the axis-cylinder." This is well shown in the annexed illustration, reproduced from his paper. If we now consider the segments as canaliculi leading from the axis-cylinder, we can readily see how the blood-plasma can penetrate the myelin and its oxidizing substance, and these bodies carry on, when brought into contact, a reaction similar to that which occurs in muscle-fiber. Indeed, if the various features enumerated are collectively considered, it will become apparent that *the myelin, or white substance of Schwann, when in contact with the oxidizing substance of the blood-plasma undergoes a reaction in which chemical energy is liberated.*

When we consider that the axis-cylinder is, as stated, the continuation of a neuron's axon, it is not difficult to account for the various phenomena, known under the general term of "nerve-degeneration,"—i.e., the disorganization of myelin, the dissolution of the myelin, etc.,—at the distal end of a nerve,

³⁵ Tizzoni: Archivio per le Sci. med., vol. iii, fasc. 1, 1878.

when the latter has been cut. Very suggestive, in this connection, are the following lines by Professor Barker³⁶: "Waller proved that if a motor nerve was severed there resulted complete degeneration of the fibers in the peripheral end, even

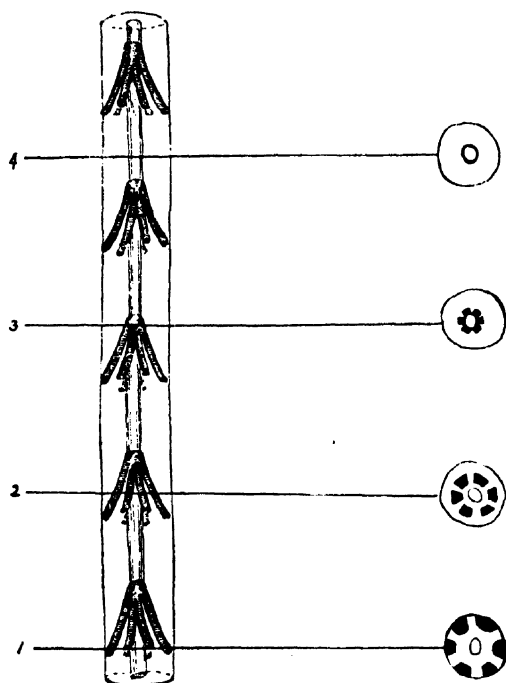


DIAGRAM OF RELATION BETWEEN LONGITUDINAL AND TRANSVERSE SECTIONS, SHOWING

1, at base of cone; 2, through middle of cone; 3, through apex of cone; 4, through interval between two cones. In 1, 2, and 3 the cone segments and protoplasmic sheaths are seen. In 4 only the thin protoplasmic sheaths beneath primitive sheath and around axis-cylinder are visible. (W. H. Wynn.)

to the muscles which they govern, the central end remaining apparently intact. As a matter of fact, the changes characteristic of the Wallerian degeneration could not, as a rule, be traced farther in the central end than to the first node of Ranvier." Stewart³⁷ states that "in the degenerated nerve

³⁶ Barker: *Loc. cit.*, p. 740.

³⁷ Stewart: "Manual of Physiology," p. 607.

the substances soluble in ether are relatively increased owing, in part, to fatty degeneration of the axis-cylinder," and that "the percentage of phosphorus is markedly diminished (Mott and Barratt)."

Another process which seems to acquire a certain degree of light is nerve-regeneration. It is obvious that if we grant the axis-cylinder, as the extension of the axon, all functional and nutritive attributes, we may easily explain peripheral nerve-degeneration, but not regeneration, the peripheral segment being unprovided for by reason of the section. We know, on the contrary, that a piece of the nerve must be removed in order to prevent reunion, and that otherwise in two or three weeks, and often earlier, its functions will be restored. New cylinders and fibrils grow, acquire myelin, and, perhaps, guided and assisted by (nucleated) neurilemma, soon meet those of the peripheral segment and become connected with them. Physiological functions of a normal kind must underlie this process even in the peripheral end of the nerve; otherwise union would not take place. Finally (we can only refer to a few of the more prominent processes involved in the vast subject now claiming our attention) the functional phenomena that follow after division of the cord distinctly indicate the continuation of nutrition and the functional activity—though impaired—in the distal fragment. Foster, for instance, says: "In the mammal (dog) after division of the spinal cord in the dorsal region regular and apparently spontaneous movements may be observed in the parts governed by the lumbar cord. When the animal has thoroughly recovered from the operation the hind-limbs rarely remain quiet for a long period of time; they move restlessly in various ways; and, when the animal is suspended by the upper part of the body, the pendent hind-limbs are continually being drawn up and let down again with a monotonous rhythmic regularity suggestive of automatic rhythmic discharges from the central mechanisms of the cord. In the newly-born mammal, too, after removal of the brain movements apparently spontaneous in nature are frequently observed. But all these movements, even when most highly developed, are very different from the movements, irregular and variable in their occurrence, though orderly and purposeful

in their character, which we recognize as distinctly voluntary." Indeed, the nervous energy that myelin and the oxidizing substance procure is that which allows a frog deprived of its hemispheres and its middle brain "to sink in water as though the animal were of lead."

The axis-cylinder composed of fibrils into which blood-plasma penetrates being continuous with the axon of a neuron, we are brought to realize the nature of the parallelism between the functional phenomena of the latter and those of the suprarenal glands to which I have already referred. But we must not lose sight of the fact that each "medullated" nerve-fiber is divided by the nodes of Ranvier into as many subdivisions, and that each internodal segment receives its own supply of plasma. Does the neuron receive its supply through this chain of segments, or, rather, through the axis-cylinder that passes through them? That the former mechanism alone prevails is improbable, since so prominent a part of the entire structure as its cell-body, the seat of its nucleus, would hardly be supplied in so indirect a manner. The very importance of its functions betokens the existence of direct supply. Does such a vascular system exist? Fortunately, we have not far to seek.

THE CIRCULATION OF THE NEURON.—Barker, in a review of the facts that have been adduced for or against the neuron doctrine,³⁸ concludes that "it may be said, with fairness, that the control instituted by hundreds of histologists in various parts of the world has practically in every instance in which the method of Golgi or the method of Ehrlich has been employed gone to confirm the conception that the neuron is a unit in the sense of Waldeyer." The latter investigator's words, giving the gist of his doctrine, are also quoted: "If we review the main advance, made certain by the anatomical investigations discussed, it lies, in my opinion, in the sharper limitation, now possible, of the anatomical as well as the functional elements of the nervous system (for such we have to consider the nerve-units-neurons), and also the discovery of collaterals, with their end-arborizations, by Golgi and S. Ramón y Cajal." The following lines of Waldeyer's are also

³⁸ Barker: *American Journal of Insanity*, July, 1898.

quoted: "If we assume, with Golgi and B. Haller, the existence of *nerve net-works*, the conception is somewhat modified, but we can still retain the nerve-units . . ."—all of which tends to show that, while the neuron doctrine stands on a solid foundation, there is a stumbling-block in its way which has not as yet been removed. Especially is this true since the investigations of Apáthy, of Naples, who, after several years' study, has unquestionably demonstrated the existence of a net-work of what he terms "neuro-fibrils."

That Apáthy's "neuro-fibrils" as well as Golgi and Haller's nerve net-works are *not* nerve-elements, but fine capillaries which serve for the circulation of blood-plasma, seems to me probable. In the following extracts the italicized words will serve to call attention to the various links between these structures and others that we have analyzed. Professor Barker summarizes Apáthy's views as follows: "Apáthy has been convinced for some twelve years that the nervous system is composed of two varieties of cellular elements entirely different from each other: nerve-cells and ganglion-cells. The *nerve-cells*, the architecture of which is quite in accord with that of *muscle-cells*, give rise, he thinks, to neuro-fibrils. A neuro-fibril, in turn, passes out of a process of a nerve-cell and then goes through a number of ganglion-cells, and ultimately, after leaving the last ganglion-cell with which it is connected, passes more or less directly to a muscular fiber or to a sensory cell. The neuro-fibrils are, as *conducting substance* for the nerve-cells, what the *muscle-fibrillæ* are as *contractile substance* for the muscle. The pathways to be followed by the neuro-fibrils are predestined from the earliest embryonic stages, for they correspond, according to Apáthy, to the *intercellular protoplasmic bridges*." That we have all required elements in support of my belief is evident; we have seen that muscle-fibers are, in reality, delicate tubes; that vascular channels for the transmission of blood-plasma should be protoplasmic is as obvious as is the need of their penetrating into and out of the cells.

What appears to me as conclusive evidence is indirectly afforded by the deductions of Ehrlich, suggested by his study of the methods of staining living nerve-cells and their processes with methylene-blue. "Ehrlich found," says Barker, "that by

injection of a solution of methylene-blue dissolved in salt solution *intra vitam* into the *blood-vessels* of an animal, the *axis-cylinders* of many of the nerve-fibers (see Fig. 1), as well as numerous (particularly sensory) nerve-endings (see Fig. 2),



FIG. 1.—NERVE-FIBERS FROM A FROG INJECTED WITH METHYLENE-BLUE (METHOD OF EHRLICH). (After Külliker.)

The axis-cylinders are stained dark blue. In places the myelin sheath is somewhat stained. The nodes of Ranvier and the divisions of the fibers at some of the nodes are well shown.

were stained after a time, when exposed to the air, an intense-blue color, the other tissue-elements remaining little or not at all affected." It seems clear that, if a solution introduced through blood-vessels can stain the axis-cylinders, the liquid

within the latter must be more or less a continuation of that in the blood-vessels. Again, I have suggested that the blood-plasma, including its oxidizing substance, was the liquid in the axis-cylinders; that this is true is shown by Ehrlich's observation that "the conditions in the nerve-structures essential to the methylene-blue reaction" were, he thought (1886): "(1) oxygen saturation; (2) alkalinity." I have shown that these are the essential attributes of blood-plasma.



FIG. 2.—SENSORY NERVE-ENDING STAINED WITH METHYLENE-BLUE (METHOD OF EHRLICH) IN THE EXOCARDIUM OF THE LEFT AURICLE OF A GRAY RAT. (After Smirnow.)

This seems to me to afford an insight into the physiological chemistry of the axis-cylinder of the neuraxon when a short distance below the latter it has become a medullated nerve. Indeed, the prevailing view that the myelin represents a protective and insulating coat may at least be said to be open to doubt, especially when coupled with the facts that its chemical composition is unknown, and that there is another external coat: the neuro-keratin neurilemma, which suggests, by its composition, that it is an isolating covering and that it also fulfills this

rôle in non-medullated nerves. That the myelin is the seat of a combustion process during which heat is liberated and a decomposition product, cholin, is formed, we have seen. If we now consider the composition of the active component of myelin, lecithin, *i.e.*, carbohydrates and phosphorus, and its analogy, as regards carbohydrates, to myosinogen, the probability that it serves as a source of energy, as does the latter when in contact with oxygen, suggests itself. That such is the case, however, is shown by the fact that the contents of the neuraxon or axis-cylinder fulfills the conditions necessary for methylene-blue staining, as laid down by Ehrlich, *i.e.*, oxygen saturation and alkalinity, the characteristics of blood-plasma. Indeed, it seems to me permissible to conclude that:—

1. *Myelin, or the white substance of Schwann, is to nerve-structure what myosinogen is to muscle-fiber: i.e., its immanent source of energy.*

2. *The axis-cylinder and the canaliculi derived therefrom are made up of fibrils that serve as channels for blood-plasma.*

3. *A part of this blood-plasma penetrates into the axis-cylinder through Ranvier's nodes.*

4. *Lecithin, a body composed mainly of hydrocarbons and phosphorus, the active constituent of myelin and a prominent component of the electric organ of the ray, when exposed to the action of the oxidizing substance liberates energy: i.e., nervous energy.*

Continuing our quotations from Professor Barker's article, I will introduce the various points of comparison which appear to me to sustain my interpretation of Apáthy's neuro-fibrils. "Inside the ganglion-cells a reticulum of fine fibrils derived from the neuro-fibrils in transit can be stained a beautiful deep-violet color by Apáthy's chloride-of-gold method." That the latter method can be considered as similar in action to the methylene-blue method and that the stain follows the same channels and affects the same chemical constituents of the plasma is shown by the following remark of Professor Barker's: "With a little care and a good sample of methylene-blue the *nerve-endings* and the *axis-cylinders* of medullated fibers, with which they are continuous, can be stained in a way far surpassing in constancy and completeness the best re-

sults of the uncertain gold-chloride procedure." As the methylene-blue and a modified chloride-of-gold stains were those mainly used by Apáthy, no confusion can occur on this score.

Indeed, if we convert all of Apáthy's neuro-fibrils into minute capillaries, their identity as inherent parts of the general circulation is placed on a solid foundation by the following remark of Professor Barker's: "The doctrine of the fibrillary nature of the axon and unstainable portion of the protoplasm of the nerve-cell has recently received support from the studies of Lugaro³⁹ and Levi.⁴⁰ The former, too, in his studies of the nerve-cell under pathological conditions—for example, after poisoning with *lead* and *arsenic*—finds that the fibrils may become very distinct in the nerve-cells." That this directly points to the one system through which the morbid changes can occur, *i.e.*, the adrenal system, and that it precisely coincides with the foregoing remarks bearing upon this system, is evident.

The similarity of the neuro-fibril, on the one hand, to the axis-cylinder and its cell-body extensions, on the other, now becomes a normal consequence. "Each neuro-fibril is," Apáthy states, "made up of a large number—near its origin, at any rate—of 'elementary fibrils,' and in the course which it follows elementary fibrillæ are being given off at short intervals until finally the neuro-fibril itself may be reduced to a single elementary fibril." The fibrillary structure of an axis-cylinder is as clearly reproduced here as it can well be; the giving off of fibrils but typifies the irregular distribution of "non-medulated" nerve-fibers, and particularly those of the "sympathetic" system.

All this recalls a structure which appears to me to be intimately connected with the general circulation, the neuraxon and its cellular extensions, and Apáthy's neuro-fibrils—all being considered as component parts of the general vascular system: *i.e.*, Virchow's neuroglia.

The prevailing view concerning the rôle of this structure is that it affords a supporting frame-work for the nervous elements. Both in the white matter and gray matter the medulated nerve-fibers are separated one from the other by a

³⁹ Lugaro: *Rivista di patol. nerv. e mentale*, vol. i, 1896.

⁴⁰ Levi: *Rivista di patol. nerv. e ment.*, vol. i, 1896.

net-work of glia-fibers. In the gray substance, however, the neuroglia, though present in greater abundance, as a rule, than in the white substance, varies considerably, the net-work of fibers being especially thick in certain parts. "The neuroglia is present in greatest abundance in the gray matter immediately surrounding the central canal of the cord and the ventricles of the brain (the ependyma, as it is called)," says Stewart⁴¹: a suggestive feature in connection with the views submitted in the present chapter. The neuroglia-cells, as is well known, are of two kinds: those provided with mossy processes and those that have smooth extensions. A large number of investigators still consider that the latter represent true processes, and that, by freely anastomosing, they make up the mesh-work which surrounds the nerve-cells and their prolongations. Ranvier, however, after a searching study of the subject, was led to conclude that the smooth processes of these (stellate) glia-cells, were in reality neuroglia-fibers which merely passed through the latter in all directions, without forming part of the cellular structure *per se*. We have seen that Apáthy's neuro-fibrils, when they left the "nerve-cell," also passed *through* the cells after forming a reticulum in the latter: a feature which suggests that Apáthy's neuro-fibril and the neuroglia-fiber may be structurally similar.

It was formerly thought that neuroglia was a variety of connective tissue, but this view no longer prevails. Indeed, so distinct is the latter from neuroglia that the two structures can be differentiated from each other by the simplest tests; thus, Ranvier and Malassez found that connective tissue placed in cold water was not modified after several days' maceration, whereas neuroglia-fibers were completely destroyed after two or three days. On the other hand, connective tissue was completely destroyed by prolonged boiling in water, while neuroglia was hardly altered under similar conditions. The suggestive relationship between Apáthy's neuro-fibrils and glia-fibers offers some ground for the belief that glia-fibers are also nervous elements. This appears to be sustained by the fact that identical results ensue when nerve-fibers and connective tissue are submitted to the last of the two tests mentioned, the

⁴¹ Stewart: *Physiology*, p. 671, 1900.

nerve-fiber being merely rendered opaque, while the connective tissue is destroyed. As the latter is gelatinous, its destruction is easily accounted for, but why should the nerve-fiber be rendered opaque? Evidently non-medullated fiber had been used in the test, for medullated fiber is always opaque, while the non-medullated is translucent. I am led to suspect, in view of my belief that the axis-cylinder of a nerve contains blood-plasma, that it is the latter which became opaque during the boiling process. This is an important feature, for it would mean that neuroglia-fibers also contain plasma.

The identity of neuroglia-fibers as plasma-channels becomes emphasized when the morbid effects of poisons upon them and upon their cells are studied. Berkley⁴² found the cell-bodies of the *vascular* neuroglia "larger, the protoplasmic extensions" being "thick and knotty and the arms extending toward neighboring vessels more prominent than in the normal." This was noted in slides derived from animals submitted to experimental acute alcoholic poisoning. When we consider that alcohol primarily stimulates the adrenal system with great violence and that the neuroglia closely invests the blood-vessels, it seems permissible to surmise that the thickenings and knots are dilations due to the centrifugal pressure of the plasma derived from the capillaries. Especially does this seem probable when the fact that "capillaries, like the intermediary vessels, are tortuous and twisted" is added to the rest of the evidence. And these alterations, besides an "exceeding abundance of the polynuclear leucocytes in and around the cerebral vessels," etc., are not peculiar to alcohol, for Berkley emphasizes the fact—demonstrated for the first time—that the lesions produced "are very similar to the pathological lesions produced by other more virulent soluble poisons": additional proof that the adrenal system underlies the morbid process. Serum-poisoning was also found to cause great swelling of the bodies of the vascular neuroglia, "thick groups of these swollen cells" surrounding "nearly all the vessels of any size in the gray layers." In ricin poisoning Berkley found the cell-bodies "universally much larger than the control," and "apparently

⁴² Berkley: Johns Hopkins Hospital Reports, vol. vi, No. 1.

swollen, even globular in outline." The extensions were also thicker and more nodular. "Are these elements, which belong to the *lymphatic* apparatus," queries the author, "taking up *detritus* from the degenerating protoplasm of the nerve-cells and becoming engorged?" The conclusion that they belonged to the lymphatic system was reached because they were found to contain *lymph*, which, in the language of Johannes Müller, is "blood without its red corpuscles": *i.e.*, *blood-plasma*, and, of course, its due proportion of oxidizing substance.

Evidently then, it is the *plasma* found in the capillaries of cellular elements of all organs which, crowded by excessive back-pressure (due to the marked contraction of the central vascular trunks induced by the poisons), causes the endothelial plates or cells constituting the walls of what Berkley terms the "intermediary vessels" to look, using his words, "as if they had been subjected to *severe strain*," as their even walls have "many irregular *bulges* in their outlines." That the neuroglia-fibers are the channels through which it is transmitted is also suggested by a remark made in connection with the effects on the gemmules, the retention of which, writes Berkley, "clearly shows that the swelling comes *from within* the substance of the stem and pushes the gemmule, which are still adherent, *outwardly* and apart."

Does a direct connection between the neuroglia-fibers and the protoplasmic processes of neurons exist, as suggested by the fact that Apáthy's neuro-fibrils are stated by him to penetrate the cell-bodies—provided his fibrils *are* glia-fibers? To establish this upon a firm basis, the thickening, bulging, etc., found by Berkley upon the vascular neuroglia must also be shown to extend to the processes of the neuron.

Golgi has expressed the opinion that the greater part of the nerve-cell—*i.e.*, the entire structure excepting the axis-cylinder—was concerned with its nutrition: a view which met with considerable dissension. Among the opponents of this interpretation was Forel,⁴³ who contended that the entire cell was simultaneously endowed with nutritional and functional attributes. This conception was defended by Ramón y Cajal,

⁴³ Forel: *Archiv für Psychiatrie und Nervenheilkunde*, vol. 1887.

and seems likewise sustained by our analysis, so far. Indeed, we have seen that the axis-cylinder, if my interpretation is sound, is able, through the presence of its coat of myelin and its plasma-containing fibrils, not only to supply chemical—probably nervous—energy, but also to undergo nutritional metabolism. Can we say the same of the cell-body of the neuron?

We have seen that the fibrils penetrate the nerve-cell, and that various poisons, as shown by Lugaro and Levi, cause them to become “very distinct.” Referring to the intracellular distribution of the fibrils, Barker says of Apáthy: “He describes the finer peripheral neuro-fibrils as follows: They are seen to enter the cell-body and passing out to the peripheral part of its protoplasm, there to break up into a complicated plexus composed of anastomosing elementary fibrils in the outer chromatic zone. From this peripheral plexus there pass through the ‘inner alveolar’ zone radial branches to the internal chromatic zone, in which is to be seen another fine plexus of elementary fibrils, which, anastomosing and converging, finally form the single strong motor neuro-fibril, which passes out of the cell through the very center of its pyriform process. In other animals studied by Apáthy there are cells with definite dendrites entirely separate from the axon and in these the cellulipetal neuro-fibrils *enter by way of the dendrites*, ramify and anastomose freely inside the cell-body, and then, reuniting, *take their exit from the cell by way of the axon*. Similar relations exist in the ganglion-cells of the vertebrates which he has studied thus far.”

This strikingly coincides with the course of the plasma-fibrils or capillaries as I interpret it. Indeed, if the fibrils enter the cell, form a plexus therein, and pass out “by the way of the axon”: fibril, plexus, and axon represent a continuous channel which must contain plasma, since I have ascertained that the axon contains this fluid. Again we obtain a clear indication as regards the path of the blood-stream: it enters by the dendrites and passes out by way of the axon. It is with the dendrites, therefore, that the vascular neuroglia-fibers found thickened, globular, etc., by Berkley in his poisoned animals must be connected. But this fact suggests that these

structures should likewise present irregular swellings under the influence of the same agencies, and that the axis-cylinder should show less, the intracellular formation of plexuses and anastomoses interposing a barrier to the too free passage of plasma. That such is actually the case is illustrated by the annexed plates by Berkley, which represent the lesions found in the neurons of the poisoned animals to which reference has been made.

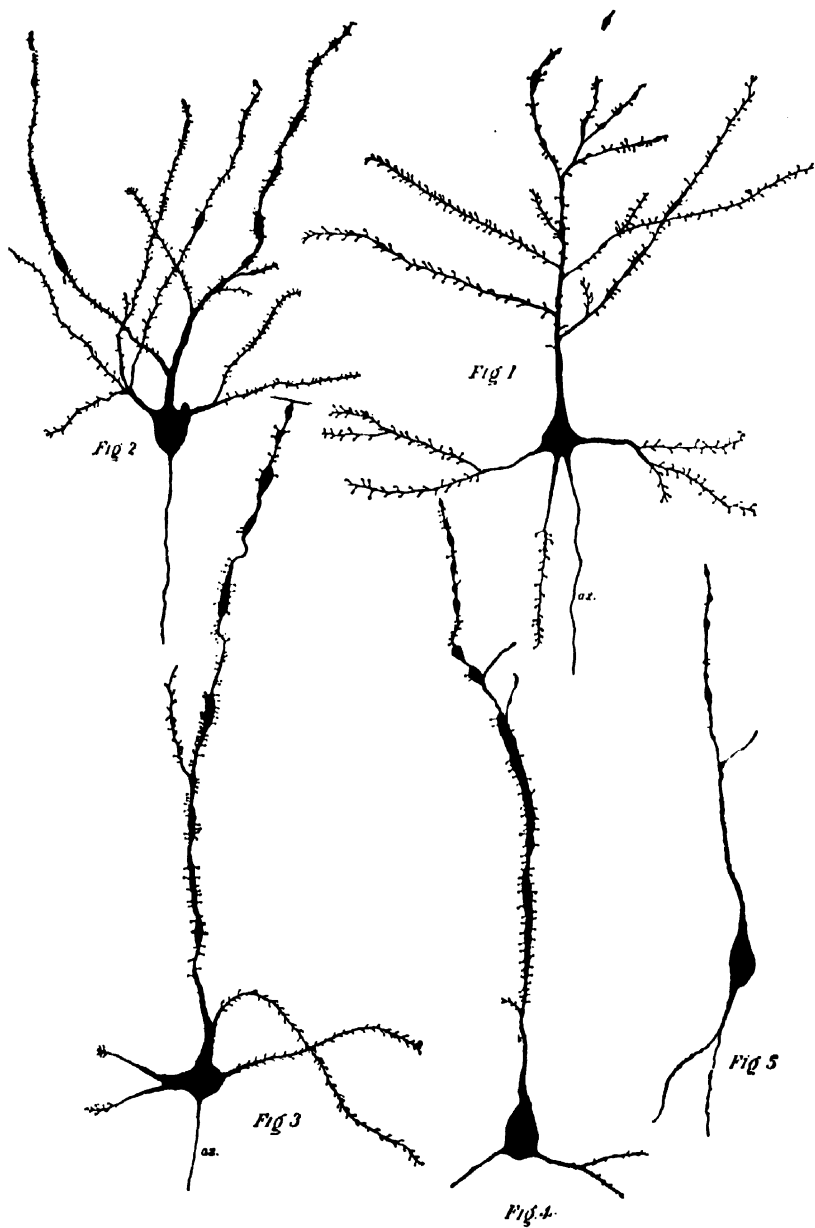
If the protoplasmic processes or dendrites are the first to bear the brunt of the vascular engorgement, the plasma being carried to them through fibrils connected with their tips, these tips or extremities should first show evidence of the expansive pressure. This is well illustrated in Fig. 1, a "*psychical* cell from the second cellular layer of the cortex," which shows, using Berkley's words, "a few pathological tumefactions on the uppermost branches of the apices of the apical dendrite. Otherwise the cell is normal." This cell was selected from a section derived from the brain of an animal poisoned with ricin, death having occurred in thirty-six hours. A feature of importance, however, is that it is the *main*, or apical, dendrite—that giving off the greatest number of subdivisions—which shows the evidences of engorgement; the extremities of the other dendrites are *not* thickened, but they show more or less marked evidences of engorgement as the main trunk is approached. This obviously suggests that the *plasma* penetrates the neuron by way of the main dendrite and that it finds its way into its collaterals cellulipetally; in other words, that, instead of also entering these collateral branches by way of their tips, it is supplied to them by the main trunk—precisely as if it were the main stalk of a plant. Of course, this does not mean that the apices of the collaterals may not subsequently show thickenings; being terminals, they should naturally do so when the pressure exceeds a given limit. This feature is illustrated by Fig. 2, especially by the larger stem of the main trunk. This cell, a projection-cell from the second layer of the cortex, shows the effects of forty-eight hours' ricin poisoning: *i.e.*, of somewhat more prolonged engorgement.

Worthy of special notice, also, is the fact emphasized by Berkley (referring to Fig. 2), that: "there is *now* distinct

diminution of the gemmulae wherever the swellings are found"—which suggests that these minute ball-tipped projections from all collaterals are structurally similar to them, and that, when the engorgement exceeds in centrifugal pressure the resistance of a given area, the walls of the latter, including the gemmules, are more or less flattened out. Suggestive, likewise, is the fact that all the gemmules stand out boldly in both preparations. As many as thirty-six or forty-eight hours having elapsed before death ensued, the animals were evidently submitted to a primary period of intense stimulation, during which the gemmules were overdistended to such an extent as to cause them to lose their retractile property. Indeed, the sudden cessation of adrenal functions and consequent death must have left the cerebral structures much as if the animals had been suddenly killed.

Of marked interest in Fig. 3 is the presence at the extremity of the main, or apical, dendrite of a section of what appears to me to represent a fiber or capillary from which the neuron with which it is connected might have derived its blood-supply. The fact that it crosses its path suggests that the dendrite itself may be a branch of the vessel. Berkley describes this neuron as follows: "Projection-cell of the long apical process variety, showing numbers of large swellings of the protoplasm of the apical dendrite, thinning of the protoplasm of the stems in the interval between the nodules, and considerable loss of the gemmulae along the margins. The lateral branches have mainly disappeared. The basal processes are retained intact."

The nodules seem to me also to illustrate the process through which the collateral fibers become detached from the main stem, as shown by the denuded cells represented by Figs. 4 and 5. The thinning of the plasma between the stems would account for the manner in which the lateral branches are detached, viz.: when the apical dendrite becomes sufficiently engorged the plasma ceases to circulate in one or more of the nodules, and the intervening protoplasm, failing to be nourished, disintegrates. That the basal processes should be the last to yield in this cell (corresponding in this with the condition of the same stems in Figs. 1 and 2) seems but normal



LESIONS IN THE NEURONS OF ANIMALS AFTER
RICIN POISONING. [Berkley.]

[Johns Hopkins Hospital Reports.]

when we consider their proximity not only to the cell-body, which contains a large supply of fibrils, but also to the axis-cylinder (*ax.* in the drawings), which is the only centrifugal channel through which the engorged plasma can escape.

A feature of the cells shown by Figs. 1, 2, and 3 which strikingly links them to the adrenal phenomena brought on by toxics in the general organism is the fact that, although they are derived from animals in which the doses of ricin injected were reduced with each animal, the morbid phenomena as exemplified by each cell in turn are correspondingly intensified. In other words, the adult rabbit represented by Fig. 1 was given subcutaneously a dose of 0.5 milligramme, and death occurred in thirty-six hours: the cell only shows apical lesions. The second adult rabbit was given the half of the previous dose, *i.e.*, 0.250 milligramme, and death occurred in forty-eight hours: the entire apical dendrite and two of the collaterals are distinctly involved. The third adult rabbit was given the half of the last dose: *i.e.*, 0.125 milligramme, and death occurred in seventy-two hours; the apical dendrite is markedly studded with thickenings, and all but two of its collaterals have disappeared. It is, perhaps, unnecessary to lay stress upon the fact that this is due to the prolongation of the excessive vascular tension: *i.e.*, of the time during which central vascular contraction caused peripheral capillary engorgement. And this need not be ascribed only to ricin. Berkley emphasizes this assertion when he says: "The poison *ricin*, whose action is in many ways *similar to that of many toxalbumins of bacterial source*, is capable of exerting a deep and extensive degenerative influence on the protoplasm of the nerve-cells of the brain." And this may further be extended to other toxics, for he also says: "Poisoning with alcohol in considerable doses, continued over a moderate time, will produce decided and ascertainable lesions of the nutrient structures and nervous elements of the cerebrum, very similar in character to the pathological lesions produced by other more virulent poisons." We thus have evidence in support of my opinion that *poisons capable of causing congestion of the cerebrospinal and other nervous tissues do so by raising the blood-pressure and by thus driving the adrenoxidase-laden plasma into their neuroglia and neurons.* That the

alterations in the elements of the neuron should be due to the same centrifugal pressure that prevails in the capillaries of all peripheral structures is obvious. Finally, the fact that phenomena witnessed occur under the influence of congestive poisons affords the complemental evidence in favor of my contention that *a neuron is directly connected with the circulation by one or more of its dendrites, which serve as channels for blood-plasma.*

Even the hæmorrhages brought on by excessive pressure, epistaxis, hæmatemesis, hæmaturia, etc., are exemplified in the engorged neuron shown in Figs. 6 and 7, and also from Berkeley's series. The observation of Apáthy's, therefore, that his "cellulipetal neuro-fibrils enter by way of the dendrite, ramify and anastomose freely inside the cell-body, and, then reuniting, take their exit from the cell by way of the axon," finds its application if, as interpreted by myself, *his neuro-fibrils are considered as blood-plasma channels.*

Still, the identity of the fibrils in the cell-body as blood-capillaries has so far only been suggested by the fact that they are continuous with the plasma-containing axis-cylinder and fibrils. While this constitutes strong evidence, the fact that they are blood-channels can only be determined by ascertaining the nature of the process in which the plasma takes part. This may probably be done by inquiring into the composition of a neuron's ground-substance.

THE PHYSIOLOGICAL CHEMISTRY OF THE NEURON.—What is the nature of the ground-substance: *i.e.*, that between the fibrils? After reviewing this subdivision of the general subject Barker says: "A neuron is made up, like all other cells, of nucleus and protoplasm. In the latter a centrosome and an attraction-sphere are present; at least it has been demonstrated in a certain number of nerve-cells. The protoplasmic portion of the cell can be roughly divided into a peripheral exoplasmic portion and a central endoplasmic portion. In neurons, as in muscle-cells, though less distinct in the former than in the latter, there is a tendency to a fibrillary structure, the fibrillæ tending to occur in the peripheral exoplasmic portion of both nerve- and muscle- cells rather than in the endoplasmic portion of the protoplasm. In both exo-

Fig. 6



Fig. 7



LESIONS IN THE NEURONS OF ANIMALS AFTER
RICIN POISONING. [*Berkley.*]

[*Johns Hopkins Hospital Reports.*]

plasm and endoplasm there can be made out in tissues which have been fixed *a more or less homogeneous ground-substance* in which are deposited larger and smaller masses of a granular nature. The ground-substance corresponds in tissues fixed with alcohol and stained by the methods of Nissl and Held to the 'unstainable substance' of Nissl, and the masses of granules to the 'stainable substance' of Nissl and the pigment.

"The 'stainable substance' of Nissl in healthy animals of the same age and species, with the same method of fixing and staining, is tolerably constant in appearance and arrangement in the *cell-bodies and dendrites* of the same group of nerve-cells: a fact of extreme importance for nerve-anatomy and pathology. The axons appear to be entirely devoid of the 'stainable substance' of Nissl. Whether the stainable substances represent bodies precipitated from solution through the action of reagents or bodies pre-existent, though invisible, first brought into view through the action of fixing or staining reagents in the hardened tissues, in either case they appear to yield the chemical tests *characteristic of the group of nuclealbumins*. Whether the staining reaction characteristic of the stainable substance depends upon chemical relations or upon purely physical conditions must, for the present, remain undecided.

"The 'unstainable portion' of the cell-body,—that is, the ground-substance,—though probably functionally much more important than the stainable, is not so well understood; its nature and structure are still as obscure as those of protoplasm in general." Still, the link with features previously brought out by our analysis now seems within reach.

Held has maintained that the stainable Nissl bodies represent simply substances precipitated from solution by the action of fixing mixtures; Fischer was led to the same conclusion. Barker says, in this connection, that he repeatedly convinced himself of the *homogeneous* appearance of the protoplasm of the nerve-cell when it is examined immediately after the removal from the living body. That the ground-substance is homogeneous, and that the unstainable portion is a product of dissociation of some of its constituents, are therefore probable. But the stainable portion we have seen has yielded the chemical

tests "characteristic of the group of nucleo-albumins." We are not, therefore, dealing with the group of nitrogenous fats to which lecithin, the main constituent of myelin, belongs, but with what probably represents, not a mere artifact, but an individual constituent which is precipitated by the fixing mixtures. It is important to determine, therefore, the exact nature of the Nissl "bodies," and perhaps by a process of exclusion ascertain that of the unstainable substance.

"Held," says Professor Barker, "undertook a most careful and exact chemical study of the granules in alcohol tissues. Thus, he found that the Nissl bodies are insoluble in dilute and concentrated mineral acids, in acetic acid, boiling alcohol, cold or boiling ether, and in chloroform. On the other hand, they are easily soluble in dilute and concentrated alkalies. With pepsin and hydrochloric-acid digestion he found that the ground-mass of the protoplasm vanished and that the Nissl bodies alone remained undigested: the reverse of what occurred on treatment with an alkali. The Nissl bodies yielded no reaction with Millon's or Adamkiewicz's reagent. Held obtained, however, slightly positive results with Lilienfeld and Monti's microchemical test for phosphorus, and a considerable quantity of the gray matter of the spinal marrow after digestion with pepsin and hydrochloric acid examined by Siegfried, of the physiological laboratory of Leipzig, showed the presence of phosphorus. Held concludes, however, from these various reactions, that the Nissl bodies belong to the group of the nucleo-albumins: a view which agrees with the investigations of Halliburton, who found in the gray matter a nucleo-albumin which coagulated at from 55° to 60° C. and which contained *as much as 0.5 per cent. of phosphorus.*"

The large proportion of phosphorus further sustains the preponderating rôle that the oxygen of the plasma must play in the neuron, owing to the activity of the reaction between these two elements. It also indicates a close relationship between the neuron and all other cellular structures of the organism. Thus, referring to Held, Barker says: "He asserts that in numerous experiments with his method (formol freezing) he has found in the *most different organs* constituents of the cell-body which behave not only tinctorially, but also mor-

phologically, *exactly* as the *stainable substance* in nerve-cells. He described them in *gland-cells*, *liver-cells*, in cells of the *pancreas*, in the cells of some sarcomatous tumors, in certain *connective-tissue cells*, but especially in normal and pathological *lymph-glands*. Cajal⁴ also asserts that the stainable substance of Nissl is not specific for the nerve-cells, as he has demonstrated its presence in certain of the *leucocytes* and of the *connective-tissue elements*." Nissl's bodies appear to me, therefore, as constituting an organized component of the ground-substance of the neuron, a nucleo-albumin rich in phosphorus, which, judging from its similarity to a large number of cellular structures elsewhere in the organism, *represents the cell-structure itself*, precisely as is the hepatic cell when free from glycogen, bile, or the agencies from which these are derived. It is to the neuron what the neurilemma, Mauthner's sheath, etc., are to the internodal segment of a nerve, and includes—as does the protoplasmic membrane of Schwann—the nucleolated nucleus.

The unstainable portion must be the equivalent of myelin: the white substance of Schwann. We have seen that this is also unstainable. Even picrocarmine does not stain it, and Ranvier states that the axis-cylinder becomes stained at the nodes because there is no myelin in this region of the nerve. The similarity between myelin of the nerves and that of the cerebro-spinal system is emphasized by Foster when he says: "Obviously the fat of the white matter of the *central* nervous system and of spinal *nerves* (of which fat by far the greater part must exist in the medulla, and for nearly the whole of the medulla) is a very complex body indeed, especially so if the cholesterin exists in combination with the lecithin, or cerebrin (or protagon). Being so complex, it is naturally very unstable, and, indeed, in its stability resembles proteid matter." This also suggests, however, that protagon, a nitrogenous body containing phosphorus isolated by Liebreich from brain-substance, may be the unstainable substance we are seeking. Hoppe-Seyler and Diakonoff, having found it to be composed of lecithin and cerebrin, the direct connection with the former is not re-

⁴ Cajal: *Revista trimest. micrografica*, vol. 1, No. 1, March, 1896.

moved. Protagon readily breaks up into its constituents. Howell states that, "while protagon seems to be regarded as the principal form in which lecithin occurs in the brain, simple lecithin is believed to be present in the nerves and other organs," and he refers to Noll,⁴⁵ who found "the quantity of protagon in the spinal cord may amount to 25 per cent. of the dry solids; in the brain, to 22 per cent.; and in the sciatic nerve, to 7.5 per cent." That it is difficult to analyze this question is suggested by his closing remark: "Regarding the synthesis of lecithin in the body, or the physiological importance of the substance, nothing is known." We have seen the important rôle that it probably plays as myelin; its presence in such large quantities, as a constituent of protagon, in the cerebro-spinal system plainly points to it as of the unstainable ground-substance of the neuron.

What is the rôle of cerebrin, which, with lecithin, forms protagon, and from which it is readily separated? In a study of the chemistry of nerve-degeneration Halliburton and Mott⁴⁶ refer to the fact that they had previously shown that in general paralysis of the insane "the marked degeneration that occurs in the brain is accompanied by the passing of products of degeneration into the spinal fluid. Of these," says the authors, "nucleo-proteid and cholin are those which can be most readily detected. Cholin can also be found in the blood." Having continued this work, they now find "that this is not peculiar to the disease just mentioned, but that in various other degenerative nervous diseases (combined sclerosis, disseminated sclerosis, alcoholic neuritis, beriberi) cholin can be also detected in the blood." The tests that they employed were mainly two: (1) "the obtaining of the characteristic octahedral crystals of the platinum double salt from the alcoholic extract of the blood"; (2) a physiological test—and a very interesting one, I may add, if the functions of the adrenal system are included in the process, namely: "the lowering of blood-pressure," which the authors consider as "partly cardiac in origin and partly due to dilation of peripheral vessels," and

⁴⁵ Noll: *Zeitschrift für physiol. Chemie*, Bd. xxvii, S. 370, 1899.

⁴⁶ Halliburton and Mott: *Journal of Physiology*, Feb. 28, 1901.

"which a saline solution of the residue of the alcoholic extract produces." This fall "is abolished," they further state, "if the animal has been atropinized." I may incidentally remark that these few lines embody the pathogenesis of most neuroses attended with degeneration, viewed from my standpoint, since we have here the phenomena incident upon arrest of function, auto-intoxication, and toxic suprarenal insufficiency. But directly bearing upon the subject in point is the evident identity of cholin as a product of degeneration. It "has its source in lecithin decomposition and putrefaction," says Howell. But it is likewise, as we have seen, a waste-product of normal nervous-tissue metabolism, being eliminated with the bile in a modified form. That *cerebrin is also a product of putrefaction and of physiological metabolism* is suggested by two facts: it is found in pus-corpuseles and its formula and that of cholin present considerable analogy. Even taking as standard that furnished by H. Müller, which has given rise to considerable controversy, cerebrin is $C_{17}H_{33}NO_3$, while cholin is $C_5H_{15}NO_2$. *Lecithin, therefore, becomes the functional ground-substance of the cell-body of the neuron, just as it is in the nerve. Both in the neuron and its continuation, the nerve, therefore, the vascular fibrils carry blood-plasma, which, by passing through their walls, maintains a continuous reaction, of which the phosphorus of the lecithin and the oxygen of the blood-plasma are main reagents and chemical energy the end-result.* The relationship between the vascular fibrils and the ground-substance, nucleus, etc., is well shown in the engraving on page 558.

But lecithin, though a useful product of metabolism, requires in its formation the aid of protoplasmic function, as does, in the muscle, the elaboration of myosinogen. In the cell-body this is probably performed, we have seen, by structures which the Nissl bodies, as nucleo-albumins, represent. Indeed, in a study of the action of fixatives upon *protoplasm* Hardy found⁴⁷ that, "when a soluble colloid is fixed by the action of a fixing reagent, it acquires a comparatively coarse structure in the process, which differs wholly or in part from the structure of the soluble colloid." Again, that these protoplasmic

⁴⁷ Hardy: *Journal of Physiology*, May 11,

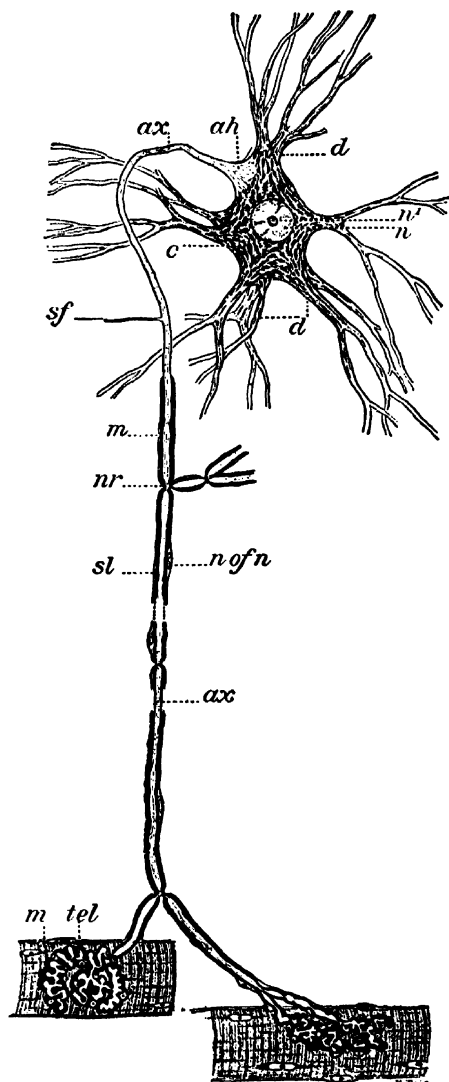


FIG. 3.—SCHEMATIC REPRESENTATION OF THE LOWER MOTOR NEURON.

The motor cell from the ventral horn of the spinal cord, together with all its protoplasmic processes and their divisions, its axis-cylinder process with its divisions, side-fibrils or collaterals, and end-ramifications (telodendria, or motor end-plates) in the muscle represent parts of a single cell or *neuron*. *n'*, Nucleolus. *c*, Cytoplasm showing the dark colored Nissl bodies and lighter ground-substance. *d*, Protoplasmic processes (dendrites) containing Nissl bodies. (Barker.)

structures are supplied by a vascular net-work similar to that of other cellular structures is shown by the observations of Apáthy, who took them for nerve-fibrils. Barker, referring to this feature of his investigations, says: "As to the relations of the neuro-fibrils to sensory surfaces, on the one hand, and muscular tissue, on the other, Apáthy makes very definite statements, especially in the last chapter of his article. A neuro-fibril entering the cytoplasm of an epithelial cell of a sensory surface in the leech breaks up (very much as in a ganglion-cell) into a *finer reticulum* composed of the *elementary fibrils*. A large number of the constituent fibrils, however, perhaps the majority, leave the cell in order to take part in the formation of a complicated *interepithelial fibril-plexus*." Neuron and nerve, therefore, appear to be similar to other organs as functional entities and to be subject to the same laws, including the circulation through them of oxidizing plasma.

This explains for the first time why tetanotoxin was found in the nerves by Bruschettini, Marie and others and why, in fact, as shown by Marie and Morax (see p. 1111), tetanotoxin, injected into the tissues, enters and ascends the axis-cylinders of nerves—an observation confirmed by Meyer and Ransom.

The rôle of the blood-plasma seems so clearly defined in the foregoing analysis that I deem it permissible to conclude that *all parts of a neuron—cell-body, dendrites, neuraxon or axis-cylinder—are channels for adrenoxidase-laden blood-plasma.*

Are dendrites provided, as are the cell-body and the axis-cylinder, with myelin? We have seen that, as stated by Barker, "the stainable substance of Nissl in healthy animals of the same age and species, with the same method of fixing and staining, is tolerably constant in appearance and arrangement in the *cell-bodies and dendrites* of the same group of nerve-cells." He also states that "the axons appear to be entirely devoid of the stainable substance of Nissl"; but Berkley,⁴⁸ referring to the nerve-fiber terminals which are extensions of the axon, writes: "The researches of Flechsig, as well as my own, have shown that these fine branches are furnished with a thin *layer of myelin* nearly to their termination." As this refers to intra-

⁴⁸ Berkley: Johns Hopkins Hospital Reports, vol. vi, p. 89, 1897.

cerebral nerve-fibers, I am brought to conclude that *the entire nervous system is built upon the same plan: i.e., of fibrils containing blood-plasma, surrounded by a layer of myelin. The main constituents of these bodies, the oxygen of the plasma and the phosphorus of the myelin, are thus brought into contact, and nervous energy is liberated.*

All this seems to me confirmed by the manner in which many, now paradoxical, phenomena are accounted for:—

The production of nervous energy, not only by the neuron, but also by the neural myelin, confirms the “avalanche” theory of Pflüger, which, though at first combated by Marey, was sustained by the latter after a series of experiments. Pflüger held that nervous excitation increased along the length of motor nerves: a view which strongly sustains my own. Duval emphasizes this fact, and states that, while the stream of impulses—which he terms “molecular vibrations,” in perfect accord with modern physics—travels 28 to 30 meters per second, it “presents the characteristic of increasing gradually as it is transmitted, i.e., as it advances in its nervous conductor.” Richet has found that excitation of a sensory nerve was more intense when transmitted from the periphery than when excitation was applied to a part of the nerve nearer to its center (Duval). It is evident, therefore, that an accumulation of energy takes place in sensory as well as in motor nerves.

My views are also sustained by the evidence afforded by nerve-degeneration. Quoting Turck's conception, Professor Barker refers to the Wallerian doctrine as follows: “Converting the Wallerian doctrine into terms of the neuron concept, the following law may be laid down: When it has suffered a solution of continuity, severing its connection with the cell-body and dendrites of the neuron to which it belongs, the axon, together with the myelin sheath covering it, undergoes in the part distal to the lesion acute and complete degeneration. This degeneration includes, not only the main axon, but also its terminals, together with the collaterals and their terminals connected with it.” If the gradual increase of energy along the nerve, just referred to, is considered as a factor of the function and the sum-total of the energy utilized and is interpreted as made up of *neuron energy plus gradually increased nerve-energy,*

the following main facts connected with nerve-degeneration seem to me to find their explanation:—

Section of a motor nerve will cause degeneration of the peripheral fragment, and atrophy of the muscles supplied by it. I have emphasized the functional importance of a continuous supply of nervous energy, both upon the vascular and cellular elements of any organ.

There is no degeneration of the upper, or proximal, fragment, however, except as far as the first Ranvier node. This has been ascribed to traumatism, but we can readily understand now that section through an internodal segment destroys the mechanism of that segment, the supply of oxidizing substance failing to reach the myelin through the fibrils and their canaliculi. Its nutritional or "passive" function is thus arrested.

That the nerve and even its neuron require some of their own energy to permanently sustain their own life, as emphasized by Marinesco,⁴ especially when long stretches of nerve are involved, is shown by the fact that if the seat of its ultimate distribution is destroyed,—a muscle, for instance,—or if it is disconnected from the latter, the nerve may, as sometimes occurs after amputations and peripheral neuritis, degenerate, and the process extend up to and include the cornual cell. That this does not always occur is doubtless due to the fact that the subdivisions of a nerve all contribute to the maintenance of its life, and that the chances that degeneration of a long nerve will occur are proportionate to the number of branches it supplies in its course.

The sensory nerves show the same attributes, but, of course, in a reversed direction. Section of the posterior root above a ganglion is followed by degeneration of the dorsal stump, which may include the extension into the cord. Amputation sometimes causes not only atrophy of the peripheral fibers, but also of the ganglion-cells and their prolongations in the columns. "The living muscle seems so organized that without nervous stimulation it can no more live than can the tropical animal without warmth or the rose without water,"

⁴ Marinesco: *Neurol. Centralbl.*, Bd. xi, 1892.

says Morel. How true this is is emphasized by the precaution Nature takes to nourish the nerve throughout its entire length and thus to insure the conversion of the chemical energy contained in its myelin and the plasma into nervous energy.

THE MINUTE CIRCULATION OF THE CEREBRO-SPINAL SUBSTANCE.—Such a circulation as that I suggest by this title is not thought to exist. Both in the central ganglionic and in the cortical arterial systems the arteries are now believed to be “terminal”: *i.e.*, to neither supply nor receive any anastomotic branch. They penetrate the cerebral substance to terminate there. The veins are similarly disposed. Deprived of valves and muscular tissue, they are likewise considered as “terminal” in the sense attributed to that word in respect to the arteries: a normal outcome of the absence of connection with the latter as supposedly indicated by the impediment presented to the injection of fluids in them. And yet, how does the blood, with its corpuscles, find its way from the arteries to the veins? Does it filtrate through the arterial walls, find its way through the lymph-spaces to the venous walls, and reach the sinuses? Of course, we have elsewhere in the organism both the effusion of plasma and the emigration of corpuscles through vascular walls; but this is a process of a different kind, and for which the blood-stream only plays the part of purveyor; it represents the main factor of a reparative and protective function, of which, indeed, the cerebro-spinal system is a prominent beneficiary when need be. There is a wide margin, however, between this process and the mechanism of circulation, which includes channels beginning at the heart and ending in this organ, and having for its purpose, not only to carry oxygen to all parts of the organism, but also to rapidly remove blood as fast as its oxygen-ratio is being reduced. “Terminal” vessels do not satisfy this *sine qua non* of perfect metabolism in the cerebro-spinal system, notwithstanding the presence in the superficial structures of more or less close capillary net-works. Indeed, the very presence of these capillaries seems to me to point to these deeper “terminals” as incongruities.

The marked evidences of engorgement so typically shown by Berkley’s illustrations, and to which I have referred, are

characterized by a suggestive feature: *i.e.*, they occur, as far as the neuroglia is concerned, in the elements adjoining the blood-vessels or connected with them. Thus, Berkley writes: "In the silver slides the support elements proper, so far as the stain shows, present *no variations from the control*, but, on the other hand, the *vascular* neuroglia gives indication that alterations are taking place within its structures, and show considerable variations from control preparations. The cell-bodies are larger, the protoplasmic extensions are thick and knotty, and the arms extending *toward neighboring vessels* are more prominent than in the normal." As "the capillaries, like the intermediary vessels, are tortuous and twisted,"—evidences of intense engorgement, further emphasized by the "closely packed" white blood-corpuscles found in the vascular lumen,—it seems but logical that the engorged capillary and the engorged neuroglia-fibers should be continuous; otherwise the latter neuroglia swelling would remain unaccounted for.

Referring to the spinal cord, Berdal¹ states that "the moment the blood-vessels penetrate into the cord they become covered, on a level with the perimedullary neuroglia layer, with a coating of neuroglia, which follows them throughout *all* their ramifications and accompanies them along their *entire* course." Such a coating over cerebral capillaries would readily account for the engorgement of both structures to which we have just referred, since the channel, notwithstanding the alteration in its external aspect owing to the assumption of an extra coat, would, after all, be continuous. That such is the case is sustained by the fact that in what has been termed "chronic ependymitis"—doubtless a condition in which the layer of neuroglia becomes permanently engorged—a marked thickening of the tissue occurs (O. Israel). The increase of blood in the neuroglia-fibers which this morbid condition involves not only coincides with the swellings observed by Berkley after various forms of poisoning, but it is accounted for by the fact that ependymal neuroglia-cells were found by Marchi to send "a central extension which penetrates into the optic thalamus, where it subdivides to become *fixed upon the walls of the blood-*

¹ Berdal: *Loc. cit.*, p. 193.

vessels" (Berdal). This recalls the interesting feature in Fig. 3 of the plate opposite page 550. In the projection-cell represented the extremity of the long and irregularly-swollen apical process is also connected with the wall of what must be a diminutive blood-channel, if plasma is at all the cause of the cellular engorgement. Again, the neuroglia-cell, shown below, copied from an article by Andriezen, to which I will presently refer,⁵¹ may be seen to be directly attached to a vessel. Indeed, we have Golgi's own testimony to the effect that some of the protoplasmic extensions of the nerve-cell are attached to neuroglia-fibers and to blood-vessels.

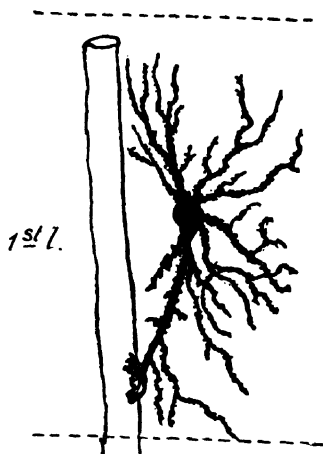


FIG. 1.—"A PROTOPLASMIC GLIA-CELL FROM A HUMAN BRAIN (FIRST LAYER OF CORTEX)." (Andriezen.)

The manner in which the neuroglia-cells and their fibers are connected with blood-vessels suggests that they are essentially different structurally, the neuroglia-elements being, not branches or subdivisions of the vascular system, but nervous structures which, at a given time during embryological development, became affixed to the vascular walls. This is sustained by the fact that neuroglia is, like all nervous elements, of epiblastic origin. Again, there is considerable analogy between nerve- and neuroglia- fibers. Foster emphasizes this fact when

¹ Andriezen: *Brain*, Winter, 1894.

he says: "Since the nerve-filaments, like the neuroglia-fibers, are very fine, and take, like them, an irregular course, it often becomes very difficult in a section to determine exactly which is neuroglia and which are nervous elements."

What is the rôle of the neuroglia and how is it functionally related to the true nervous elements? Suggestive, in this connection, are the following lines of Professor Foster's: "A medullated nerve-fiber of the white matter of the spinal cord resembles a medullated nerve-fiber of a nerve in being composed of an axis-cylinder and a medulla; but it possesses no primitive sheath or neurilemma. This is absent, and, indeed, is not wanted: *the tubular sheath of neuroglia* affords, in the spinal cord (and, as we shall see, in the *central nervous system generally*), the support which in nerves is afforded by the *neurilemma*."⁵² This shows conclusively that for a certain distance, at least, the neuroglia-sheath and the myelin act as coats for the one axis-cylinder: *i.e.*, for the fibrils containing blood-plasma. But we have seen that myelin is not the passive insulating substance that it is now thought to be; if my views are sound, it represents one of the two most important factors of nerve-composition, and, indeed, the main source of nervous energy. In modifying the accepted view concerning its functions, however, I have eliminated its rôle as insulating layer, leaving nothing but the neurilemma, or external, tubular investing sheath, for the protection and insulation of the "battery elements," as it were, the myelin and its oxidizing plasma. It is, therefore, this protective and insulating sheath that the neuroglia replaces in the white substance of the cord and in "the central nervous system generally": *i.e.*, wherever the myelin and its inclosed blood-plasma are present in the cerebro-spinal axis.

We have seen that, according to Barker, and as shown by the researches of Flechsig and Berkley, the dendrites of neurons are furnished with a thin layer of myelin nearly to their termination; while I have shown,—conclusively, I now believe—that their central canal contains blood-plasma. We have precisely, therefore, the structure of a nerve, minus its neu-

⁵² All italics are my own.

rilemma. Indeed, the similarity even extends to the subdivision of the dendritic central canal into fibrils, for Berdal says, referring to the dendrites: "These prolongations seem striated longitudinally as is the cell, and appear to be composed of fascicles of fibrils which are continuous with those of the cellular body." A single structure is missing, however, that which, we have just seen, is represented by the neuroglia in cerebrospinal nervous elements: *i.e.*, the neurilemma. Obviously, the absence of a protective insulating sheath around the cell-body of the neuron and its extensions, considering their functional importance as generators of nervous energy, becomes absolutely incompatible with existing conditions, since the myelin would thus be exposed externally. Indeed, that the cell-body and its dendrites are supplied with an external sheath is shown by the following lines of Berkley's⁵³: "Around the body of the cell we find an insulating mass of fluid contained in the pericellular lymph-sac, and as a capsule to the sac there appears a slight condensation of the tissue at this point that would take the place of a retaining membrane. This membrane apparently terminates where the first of the gemmule are thrown off from the ascending portion of the primordial process, and likewise at the location where the first buds appear on the basal dendrites. Does the insulating fluid and covering really end at this point? In absolute-alcohol sections of the cortex of the cerebellum taken parallel with the surface and stained with the anilines, particularly the blue-black, it is *quite readily demonstrable* that the thin membrane, which is now *undoubtedly composed of fine glia-filaments*, does not really cease at this point, but becomes attenuated, and continues to ascend *and cover the protoplasmic prolongations* of the cell." This plainly shows that *the cell-body of the neuron and its dendrites are supplied with a covering which is to them what the neurilemma is to nerve-fibers; this covering is similar to that investing these nerve-fibers: i.e., a sheath of neuroglia.*

This only affords, however, information concerning the neuroglia supplied to the neuron *per se*, and to the structures which the axons become a short distance below the cell: *i.e.*,

⁵³ Berkley: *Loc. cit.*, pages 90 and 91.

nerves. But we have still to study an important question: *i.e.*, the identity of the intermediary fibrils of neuroglia—important in the sense that it has a certain bearing upon the concordance between the older views of Gerlach and the modern observations and conclusions of Golgi. Indeed, if the entire cerebro-spinal axis is made up (as far as true nervous elements go) of these medullated glia-covered nerve-fibers and dendrites, we may well conclude with Gerlach that nerve-cells are united by an intricate net-work of extremely delicate nerve-fibrils. If, on the other hand, the cell-body, its dendrites, and its axon are alone medullated and glia- or neurilemma- covered, the connection *with the vascular system* being established by *non-medullated fibrils*, I am in accord with Golgi, who denies the existence of any connection through nervous structures between neurons.

That Golgi's view prevails is suggested—provided my own view that fibrils are plasma-channels is accepted—by the following lines by Professor Foster: "The larger part of the gray matter consists, besides a neuroglia supporting the nervous elements, of *nerve-filaments* running in various directions and forming, not a plexus properly so called, but an interlacement of extreme complexity." If the italicized words "*nerve-filaments*" are converted, in accordance with my view, into *neuroglia-fibrils*, the rest of the quotation will lead us to the solution of the question: "These filaments are, on the one hand, the fine *medullated* fibers spoken of above as being recognized with difficulty, and, on the other hand, *non-medullated* filaments ranging from fairly wide and conspicuous naked axis-cylinders down to fibrils of *extreme tenuity*, the latter arising apparently either from the division of axis-cylinders and nerve-fibers passing into or out of the gray matter or from the continued *branching of the nerve-cells*."

The solution, it seems to me, lies in the fact that non-medullated fibrils exist at all, and that these range from fairly wide *axis-cylinders* down to fibrils of extreme tenuity, some of which, at least, appear to originate from dendrites. Indeed, this indicates that these non-medullated fibrils (of neuroglia, as stated by Berkley) represent the continuation of the main, or apical, dendrite (or dendrites, for there are often more than

one). Since these neuroglia-fibers are deprived of myelin, they cannot serve as sources of nervous energy, and merely represent, therefore, delicate channels through which blood-plasma, obtained by them directly or indirectly from a so-called "terminal" capillary, finds its way to the apical, or main, dendrite. The conclusion which this imposes seems to me self-evident: *A neuron is an autonomous organ as a source of nervous energy, and is supplied with blood-plasma through non-medullated neuroglia-fibrils, which are continuous with the external covering of its apical dendrites.*

Are Apáthy's fibrils, which, in the leech and earthworm, were found by him to penetrate the cell-bodies of neurons, the neuroglia-fibrils just studied? Gerlach, Haller, and others have also referred to the existence of delicate nervous networks connected with the cells. The mere transformation of these fibrils into plasma-channels has enabled me, we have just seen, to link them with all the other elements of the function studied. In other words, I simply converted the fibrils into neuroglia blood-channels and found them to satisfy the requirements of the latter. Apáthy found that a neuro-fibril passed out of "a process of a nerve-cell": there is no fibril other than the neuroglia-fiber that is continuous with the apical dendrite that this neuro-fibril could represent. The neuro-fibril was found by Apáthy to be composed of "elementary fibrils": we have seen that this is precisely the arrangement within the neuroglia-fibers. He states that in their course "elementary fibrillae are being given off at short intervals, until finally the neuro-fibril itself may be reduced to a single elementary fibril": I have quoted the statement of Professor Foster's that, as regards the "fibrils of extreme tenuity,"—those we found to act as neuroglia neurilemma,—they arose "apparently from the division of axis-cylinders." Finally, the neuro-fibrils, after freely anastomosing in the cell-body (having entered by way of the dendrite), are stated "to take their exit by way of the axon." This seems to me to indicate clearly, in addition to the evidence adduced in the foregoing pages, that *Apáthy's neuro-fibrils and the various networks thought to be composed of nerve-fibers by Gerlach, Golgi, B. Haller, and others represent the one and same system of neuroglia-fibrils, some of which*

contain myelin and blood-plasma and may, therefore, be considered as nerves, while others only contain plasma and are, therefore, blood-channels.

Under these circumstances, are the above-mentioned investigators not justified in considering the net-works referred to as nervous structures? They would be justified in doing so, did *all* the neuroglia-fibrils contain myelin; but it is the *absence* of this compound in the fibrils that serve as channels for plasma between blood-vessels and the apical dendrites of the neuron which seems to me to neutralize their view. Were there any evidence that a medullated fiber of any kind connects any portion of the cell with another structure capable of converting chemical energy into nervous energy, the question would remain an open one; but such is not the case; the absence of myelin in the neuroglia-fibrils connecting the neuron with the source of its blood-supply seems to point distinctly to the need of its absolute isolation, not only to avoid the promiscuous dispersion of the nervous energy it is able to produce, but also to enable it to store this energy and to direct it in the physiological paths.

The presence of the non-medullated fibers among the cerebro-spinal nervous elements becomes evident when the structural difference between the gray matter and the white matter is interpreted from the standpoint of my view. "Owing to the relative abundance of white refractive medulla," says Professor Foster, "the white matter possesses in fresh specimens a characteristic *opaque* white color; hence the name." . . . "In transverse sections of the cord *nearly the whole* of the white matter appears, under the microscope, to be composed of minute circles, the transverse sections of the longitudinally-disposed fibers." . . . "The *gray* matter, from the relative *scantiness of medulla*, has no such opaque-whiteness, is much more *translucent*, and, in fresh specimens, has a gray or rather *pinkish-gray* color, the reddish tint being due to the presence partly of pigment and partly of blood, for the *blood-vessels* are much more abundant in the gray matter than in the white." That in the cerebral cortex, for instance, these vessels should represent the starting-point of the neuroglia non-medullary fibrils needs hardly to be emphasized. They are now

termed "terminal," but their appearance as such is readily accounted for by the fact that here, as in the cord, they are said to be imbedded in neuroglia, whereas, in reality, the latter, composed, as it is, of a mass of diminutive fibrils, is directly *affixed* to the vessel, acting precisely as would a multitude of minute subdivisions of the vessel itself. Each fibril (in which the blood-stream is so slender that it only appears "pinkish" through its translucent covering) is, in fact, a composite counterpart of the ependymal fibril and other neuroglia structures to which I have referred. In other words, *each neuroglia-fibril is affixed to the wall of the vessel either directly or through the intermediary of a neuroglia-cell, and therefrom extends to the main, or apical, dendrite, or dendrites, of some neuron.* In addition, however, this enables me to conclude that *a neuron receives its nutrition and its oxidizing substance directly from the general circulation, and that the blood which enters by way of the apical dendrites is distributed to the free dendrites and to the cell-body.*

A question suggests itself in this connection, however, viz.: How does the blood in the collaterals return to the main dendrite to find its way with the latter's blood into the cell-body? This appears to me to find its explanation in the following (already quoted) sentence, in which Berkley describes the cell-body: "Around the body of the cell we find an insulating mass of *fluid* contained in the *pericellular lymph-sac*, and as a capsule to the sac there appears a slight condensation of the tissue at this point, that would take the place of a *retaining membrane.*" The retaining membrane is doubtless the neuroglia covering of the collateral, as it is of the entire cell; underneath, therefore, is the lymph-sac—which I consider as a plasma-sac. But we have seen that Flechsig and Berkley's researches have shown that these "fine branches are furnished with a thin layer of myelin nearly to their termination." That this myelin must, as elsewhere, be supported by the neuroglia covering and in contact with it is evident: a feature which relegates the plasma toward the center, though in contact with the myelin. If we now recall the fact that fibrils have also been discerned even in these delicate collaterals, it becomes a question whether they serve to transmit plasma, centrifugally or centripetally. As

Berkley's experiments have shown that they become the seat of swellings under the influence of poisons, there must be no escape for fluids through their walls; indeed, gemmulation would become impossible were the centrifugal pressure necessary counteracted by the escape of the plasma into lymph-spaces. That the blood returns toward the cell-body and through some of the central fibrils is therefore probable. Under these conditions I can submit, as a working proposition, that *the plasma which enters the collaterals is returned to the apical dendrite, and to the cell-body with the blood of the latter. The blood of the cell-body then passes out through the axon.*

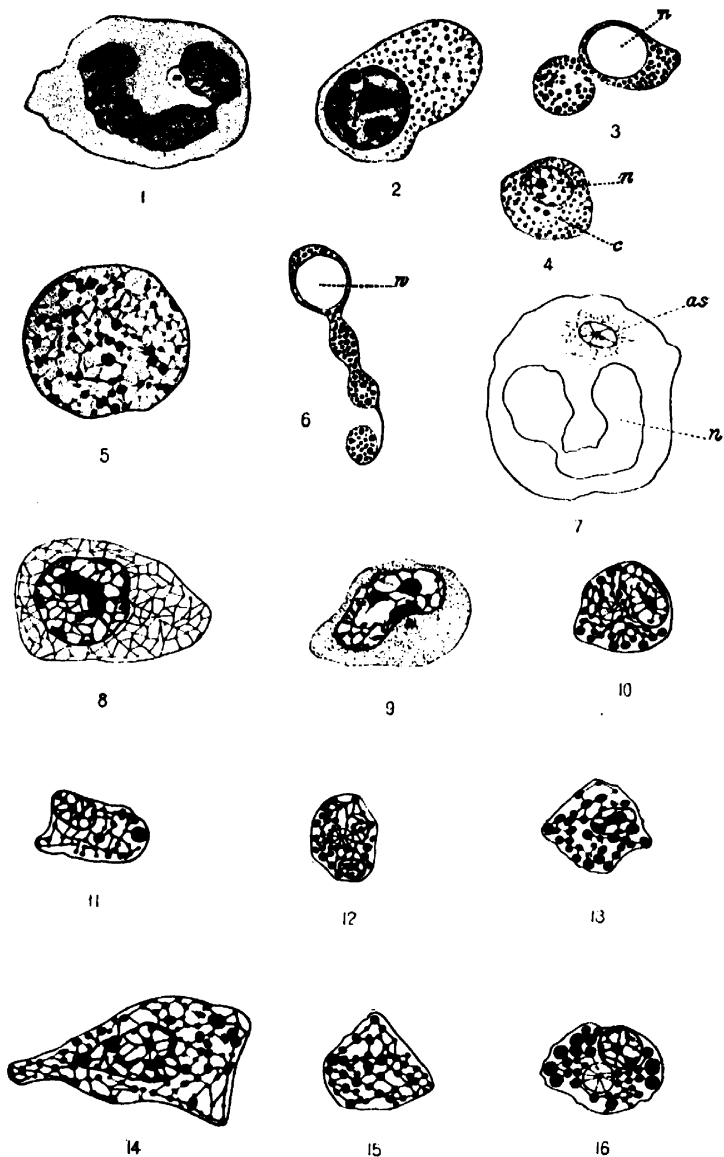
How does the blood leave the axon of the neuron in the substance of the brain and cord? This question plainly resolves itself into the following: How does the blood reach the veins from the axon? "The perivascular lymphatics . . . are especially found in connection with the vessels of the brain" says Gray⁵⁴; "these vessels are inclosed in a sheath which acts as a lymphatic channel, through which the lymph is carried to the subarachnoid and subdural spaces, from which it is returned to the general circulation." This familiar fact would be unexplainable after the views I have advanced concerning the circulation of arterial blood were the return of blood to the veins not the purpose of the lymphatic *sheaths*, for the same authority states that lymphatic *vessels* "have not at present [1901] been demonstrated in the dura mater or the substance of the brain." Again, when we consider that *perineural*, as well as *perivascular*, spaces exist, we are brought to realize that by linking the axon of a neuron to a venule, with a lymphatic space as intermediary, we have the elements of a mechanism which not only utilizes structures that are *known* to be present in the cerebro-spinal axis, but which also satisfy the needs of the function. Finally, if an axon is itself buried (up to the neck of its bulbous terminals) in a perineural sheath, which in turn communicates with a vein through stomata, as is the case in nerves, the blood of the axon is provided with a clear path to the general blood-stream.

That the blood of the neuron is eliminated as it is in other

⁵⁴ Gray: *Loc. cit.*

nervous structures—*via* the axon—is evident; but do lymph-spaces connected with *veins* actually receive this blood? Referring to the effects of acute alcoholic poisoning upon the veins, Berkley says: “Changes in the coats of these vessels are similar to those in the arterial system, but aggregations of dying polynuclear corpuscles are more frequent, and are by far the most striking feature both of their contents and surroundings. These aggregations, which may vary from three or four to a dozen or more, are located both *within* and *without* the lumen of the vessel (especially the smaller ones). Within the lumen are collections of white corpuscles filling the interior, and numbers are seen *penetrating the walls*. So vast are the collections in the *perivenous spaces* that the whole cavity is occasionally filled, and backward pressure from the plugs and compression of the vessel from the outside have attained such a height that in a number of instances the vessel’s walls have ruptured and *red corpuscles* are intermingled with the white and fill the space completely.” These features are well illustrated in the annexed photographs. The center of Fig. 8 shows “polynuclear leucocytes in the perivascular space of a small intermediary vessel compressing its walls,” while Fig. 9 shows “leucocytes in the blood in a cross-section of a large vein.” The fact that the leucocytes are found in the “perivenous spaces” and “within the lumen of the vessel,” coupled with the observation that they are “seen *penetrating the walls*,” so clearly point to the process involved that the following conclusion imposes itself: *The blood* (we have seen that even *red corpuscles* are present) *of the axon evidently finds its way into a lymph-space connected with a vein, thence to the general circulation.*

Still, there is a feature of the whole process which requires elucidation. Why should the *veins*, which, of course, communicate with channels through which the blood can be freely evacuated, become *engorged* under the influence of the adrenal stimulation induced by alcohol? Engorgement of the arteries, their capillaries, the neuroglia channels, and the dendrites is a normal consequence of adrenal stimulation; but, the veins being outlets, such is not the case with the venous engorgement. This anomaly is accounted for by the now generally admitted fact that the vessels of the cerebral substance *per se*



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are not supplied with vasomotor nerves. "Vascular nerves may be found without trouble or difficulty in muscles, glands, etc., by the silver and other stains," writes Berkley, "but in the substance of the encephalon they are never to be seen with similar staining methods; hence it is fairly reasonable to suppose that they are not present in this location and that some other controlling mechanism takes their place. I have most carefully looked for them in many brains, both human and of the lower animals, but have never seen the slightest trace of their presence within the nervous structures. . . . Tuke and Andriezen, who made researches in the same field, have also failed to find them." As I will have occasion to show, this is an extremely important factor in the pathology of all toxæmias, mental and nervous diseases, for it indicates that *any marked rise of blood-pressure due to toxics, drugs, etc., causes vascular engorgement of the vascular channels of the brain-substance simultaneously with the engorgement of the peripheral capillaries of the other parts of the organism.*

Under these conditions contraction of the central vascular trunks through excessive adrenal activity causes not only congestion of the surface, but also of the brain. Strikingly confirmatory of this fact are the following statements of Professor Foster's: "It is argued that, in the absence of vasomotor nerves of their own, the cerebral vessels are wholly, so to speak, in the hands of the general motor system; so that when the blood-pressure is high, owing to a large vasoconstriction in the abdominal viscera, more blood must necessarily pass to the brain, and when, again, the pressure falls, through the opening of the splanchnic flood-gates, less blood necessarily flows along the cerebral vessels." . . . "Again it has been observed that certain drugs have an effect on the volume of the brain quite incommensurate with their effect on the vasomotor system."

If this testimony is sound and the interpretation of the data available is exact,—my conception of the neuron's inherent functions coincides with some of the main conclusions reached by Deiters, Gerlach, Golgi, Forel, and Cajal. In outlining their conclusions, however, I will only refer to those which are directly connected with my views, as a general review would take up too much space.

Deiters (1855) affirmed the prevailing theory—undemonstrated at the time—that the nerve-cell was supplied with two kinds of processes, the protoplasmic and the nervous, the latter constituting the nerve-fiber. Gerlach confirmed the views of Deiters, and showed that the protoplasmic processes subdivided into a fine reticulum, which, he thought, anastomosed with that of other cells. Golgi then demonstrated that, besides the two kinds of processes described by Deiters, there were given off collateral processes which, with the nerve-process, or axis-cylinder, constituted the only truly nervous structures of the cell, the other processes and the cell-body being purely nutritional. The subdivisions of the protoplasmic processes or anastomoses were not, in his opinion, continuations of those of other nerve-cells, either by continuity or through nervous networks, though some of the protoplasmic extensions were connected with neuroglia-fibers and blood-vessels. Forel contended that the entire cell and its processes were simultaneously functional and nutritional. Ramón y Cajal concluded that networks of nervous fibrils did not unite the collateral processes, and, these being absolutely free, there could be no continuity of nervous substance between them, contiguity of their extremities alone prevailing.

I need hardly emphasize the fact that Golgi's views are strikingly confirmed by my own; indeed, had this great histologist converted the neuroglia-fibrils connected with blood-vessels into blood-channels, our interpretations would have been similar, though reached from entirely different directions. And I must admit that I consider this striking similarity, apart from the single line of research to which I have devoted all these pages,—*i.e.*, the histological chemistry of the circulation of the nervous system and the manner in which nervous energy is produced,—as a strong indorsement of my own conceptions. While Forel is fully sustained by my analysis when he asserts that all the parts of the neuron are simultaneously functional and nutritional, Golgi is likewise fully sustained when he considers the collaterals and the axon as the truly nervous structures, the others being nutritional. We have seen that the dendrites connected with the neuroglia-fibrils are really blood-channels. True, they are covered with gemmules

and lined with myelin, a feature which shows that they serve for the formation of nervous energy; yet this energy is not utilized in these dendrites, but by the collaterals, in addition to that elaborated by their own myelin. Nor is the greater part of the blood which courses through the main dendrites used by them; it passes into the cell-body: a great center for the *production*, we have seen, of nervous energy, which energy is mainly utilized, not by the cell-body *per se*, but by the dendrites and the axon through which the whole neuron's blood is continuously passing.

Golgi's observation that some of the protoplasmic processes were connected with neuroglia-fibers and blood-vessels furnishes histological proof that my interpretation of the manner in which the neuron is connected with the circulation is based on solid premises. The prevailing ideas, however, as to the nature of *neuroglia* normally suggested that his views included a nervous net-work as intermediary between cells, neuroglia-cells being likewise considered as truly nervous structures. Hence the affirmation of Cajal that collaterals were totally independent of one another, especially if he gave neuroglia-fibers and cells the credit of only being what they are now generally thought to be: *i.e.*, a "peculiar ground-substance," in which the "blood-vessels, the nerve-cells, and nerve-fibers" are "imbedded." The neuron is autonomous functionally: *i.e.*, as a nervous organ, *each neuron is connected with the circulation by its own neuroglia blood-channels*. An illustration of the continuity of neuroglia-fibers with the cerebral circulation is afforded by Berkley's experiments with alcohol. "Besides the swellings in the course of the dendrons," says this author, "we must always be on the watch to exclude certain processes of the support neuroglia-cells that traverse long distances of the cortex and exhibit a *pearl-string* swelling in the course of the fiber."

Are nerve-cells contiguous, as thought by Cajal? Berkley states that the great Spanish investigator writes "that the ascending fibers of the cortex, which have a vertical or oblique course through the medullary layers, have their points of contact with the protoplasm of the dendritic structures in the *intervals* between the short transverse processes (*gemmulae*)

around which the ascending fibers twine." In other words, the tips, or extremities, of the axon of one neuron, instead of being in contact with the tip of the gemmule, touch the intervals between gemmules. "Such a discharge of the nerve-forces from cell to cell taking place at hundreds of indefinite points," continues Berkley, "could not fail to produce stimuli that would be more often aberrant than direct, and, in all likelihood, such an arrangement would produce the utmost confusion of thought and motion, a veritable inco-ordination of the cerebral functions, which would reduce direct cerebration to a nullity." This point seems to me to be well taken, and the identical argument prevails as regards contiguity, for if, as I believe, myelin and the oxidizing substance are constantly in contact in the neuron,—*i.e.*, the cell-body, dendrites, and axon,—nervous energy is continuously being formed, and promiscuous contact with the dendrites of other cells would give rise to the untoward effects enumerated. In the light of my views, therefore, continuous contiguity between neurons through their dendrites or axons does not appear possible.

How do neurons transfer their nervous energy to other neurons? Berkley states that it is "more than probable that it is only at the free bulbous terminations of the nerve-filaments [axons] that we have naked protoplasm, and from this uncovered nervous substance the dynamic forces, generated in the corpora of the nerve-cells, are discharged, through contiguity, on to the protoplasmic substance of other cells. Thus, in contradistinction to the hypothesis of Cajal," continues the author, "we have only comparatively few points at which the nervous forces may discharge themselves from axons to the protoplasm of other cells, and these are seated at definite points on the terminal arborizations of the nerve-filaments, for otherwise what would be the necessity of a terminal apparatus were the nerve-conductors free to discharge their dynamic forces at any point at which they came in contact with the substance of a dendron?"

It seems to me that the feature to ascertain in this connection is the character of the functions of the gemmules. Why do these little projections of the dendritic walls become erect during the cerebral congestion induced by poisons? Are they

really intended to receive discharges of nervous energy from the bulbous tips of axons? They outnumber the axonal end-organs out of all proportion. Indeed, their multiplicity around all the stems excepting the axon hardly points to them as terminals endowed with such important functions as those attributed to them. Again, Berkley states that "the twigs of the dendrites and the fibers touch each other frequently and in a manner that appears to be perfectly indifferent for the different kinds of nervous substance, receptive and projective." Such promiscuousness plainly testifies, it seems to me, against the identity of the substances in contact being exposed surfaces capable of transmitting to each other a stream of nervous impulses.

In the light of my views, however, a function perfectly in keeping with the experiments of Goddard in puppies, of Demoor with morphine, of Berkley with alcohol, ricin, serum, etc., suggests itself. We have seen that during functional activity the gemmules project, while during inactivity they recede. If we now connect these facts with the presence in the gemmules of a thin layer of myelin immediately under their external or limiting covering, and concede that the latter and the myelin take part in the formation of each gemmule, it will become evident that during the erethic state the surface of myelin exposed to the action of the oxidizing substance of the plasma will be greatly increased and the proportion of nervous energy produced correspondingly augmented. Retraction of the gemmules, on the other hand, by emptying them of their plasma, will normally cause diminution of energy-production, the myelin of the main channel sufficing to sustain nutritional functions during sleep, for instance, when the gemmules are retracted. We have what seems to me a counterpart of these minute structures in the muscle-cell, the myosinogen of the latter being replaced by the myelin. We have also, in the processes outlined, an *active* and a *passive* functional stage in keeping with other organs. All this so thoroughly coincides with the various attributes which the gemmules have been shown by various investigators to possess, that I feel warranted in concluding that *the gemmules are peripheral extensions of the dendritic walls having for their purpose to increase, when erect, the area of*

myelin exposed to the action of the oxidizing substance of the plasma, and thus to render the dendrite functionally active: i.e., able to transmit or receive nervous impulses. When the gemmules are retracted or collapsed, therefore, functional activity is in abeyance, as during sleep, anaesthesia, etc.: i.e., they are unable to transmit or receive impulses.

This tends to show that none of the gemmules serve *per se* to transmit impulses, and that the dendritic tips must alone be endowed with this function. That such is the case seems to me suggested by Fig. 2 on the plate opposite page 550, which exemplifies the condition of a dendron before the engorgement induced by ricin has become far advanced: *i.e.*, at a time when the dendron's lumen has not as yet become completely blocked. The two central dendrites may be seen to terminate with bulbous tips, while the remaining gemmules immediately adjoining the latter are not apparently enlarged. This would point to the enlarged extremity as a dissimilar structure in respect to the gemmules, a terminal organ as it were. Again, the gemmules and terminal organ would have presented a certain degree of resemblance under the influence of the engorgement under the action of poisons, had they been similar; their appearance, on the contrary, suggests dissimilarity. Berkley states that, "so far as the end-apparatus of the collaterals from the psychical cells is concerned, the terminations of the intermediary cells, the fibers entering from the medullated masses, all have the same end-apparatus, which consists solely of a simple freely terminating *bulbous ending*, situated upon the *extremity* of the finest branches of the nerve-fibers." As he then refers to figures in one of his illustrations which represent axons supplied with bulbar extremities, I infer that it is to the dendritic terminals that he alludes, and not to those of the gemmules, as a broad application of his preceding paragraphs might suggest. If the bulbous terminals of the entire dendrite as well as the axon are referred to, the quoted lines afford additional evidence tending to show that the dendritic extremities alone transmit or receive impulses. Indeed, in the article in which chronic alcoholic poisoning is studied, Berkley remarks: "The process of tumefaction *always* appears to begin at or near the fine extremity of the dendron, be it the

extremity of the main apical process or one of its *collateral* branches, and not infrequently the *extreme termination* of the dendron, is seen to be somewhat swollen *when no other portion of the cell is involved*.⁵⁵ He also states that "in his description of the mode of ending of the *collaterals* of the great pyramidal cells" Cajal "describes their finest branches as terminating freely by a *nodosity*." All these facts seem to me to warrant the conclusion that *each of the collateral dendrites of a neuron and each axon, or subdivision of the latter, is supplied with a bulbous end-organ*.

How is an axonal end-organ of one neuron functionally related to that of a dendrite of another neuron? Berkley, alluding to the subdivisions of the axon, each of which is supplied with its bulbous end-organ, says: "These spherical apparatuses are closely adjusted against the bulbous tips of the gemmules, at times the approximation being so close that the impression is given of actual contact, though it should be remembered that the slightest overlapping will produce the same effect; and, on the whole, it is more probable that there is no actual contact, but that the *axonal discharges* of the stimuli overleap the infinitesimal distance between bulb and gemmule." For the reasons adduced, I do not think that the gemmules serve for the reception of impulses. These reasons also suggest that each axonal end-organ can only discharge its stream of impulses into the bulbous *terminal* of a neighboring dendrite, which bulbous terminal would, under these circumstances, present some analogy with the end-bulb of Krause, and, indeed, with several peripheral sensory organs. I have also submitted reasons that seem to me to offset the assertion that the end-organs actually touch. Indeed, that an "infinitesimal distance" between the efferent axonal end-organ and the efferent dendritic end-organ exists seems to be the only conclusion warranted by the histological picture, as described by Berkley. It seems to me, in other words, that *each of the bulbous end-organs of an axon, though apparently in contact with the end-organ of one of the dendrites of a neighboring neuron, may be separated from it by an infinitesimal distance*.

⁵⁵ All italics are my own.

The bearing of this arrangement, as an element of function, asserts itself when the stress we have laid upon the *vibratory* character of a nervous impulse is recalled. When studying the nature of the functional activity of muscles, I had occasion to say, referring to the governing action of motor nerves: "As the vibratory rhythm of the impulse and that of the muscle always correspond, any variation of rhythm by the brain-center correspondingly modifies the muscular contraction." If we now analyze what this vibratory rhythm means when the dendritic end-bulb and the axonal end-bulb are separated by an infinitesimal distance, but one answer appears to suggest itself: *i.e.*, that there can be no flow of impulses from one to the other. But we must not lose sight of the fact that the contradictory histological pictures described by Cajal and Berkley are those of *non-living* cellular elements, and that death may leave the two end-bulbs juxtaposed, as seen by Cajal, or separated by an "infinitesimal distance," as seen by Berkley. Thus, each histologist is right in his way as regards dead tissue. But what of living structures? Cajal and Berkley will again assist us in reaching a deduction in this connection, for *each* investigator furnishes one-half of the main physical *function* involved: *i.e.*, *vibration, which means rapidly alternating juxtaposition and separation of the bulbous end-organs.*

The rapidity with which the gap between the two terminals is opened and closed—*i.e.*, the *rhythm*—regulates, we have seen, functional activity. But can we conclude from this that non-activity of an organ means cessation of vibration of the bulbous end-organs involved in the function? We have seen that the nutritional processes of all tissues are continuous, nervous energy being supplied to the cellular elements as long as life lasts. Forel, as stated, was led by his admirable investigations to the conclusion that "living muscle appears to be so organized that without nervous stimulation it can live as little as the tropical animal can without warmth or the rose without water." This applies to all living tissues: a feature of the problem which necessarily implicates the continuous *development* of nervous energy and, as a consequence, an unceasing vibration of the end-organs. It seems to me, therefore, that, *inasmuch as the nutritional processes of the organism require a continuous*

supply of nervous energy, all the systemic axonal and dendritic end-organs are in a state of constant vibration.

Analyzing muscular contractility, I stated that: "The impulse-wave [and the blood supplied the cell] simply sets the muscle-elements to a given vibratory rhythm, and they retain this whatever be the intensity of the exertion required. . . . This may aptly be compared to the manner in which a note on a violin is made loud or soft. The power with which the string is pressed upon with the moving bow modifies the intensity of the sound; but the note remains the same. This means that its pitch does not vary, and if, for example, the lower C is given, we will know that the sound-wave of that note represents two hundred and sixty-one vibrations per second. So may the *impulse-wave* transmitted by the brain through a 'motor' nerve be represented by a fixed number of vibrations. Retraction, the muscle being then most tense, is therefore characterized by the greatest number of vibrations." If this interpretation is sound, it is likewise applicable to the "to-and-fro" motions of the bulbous terminals which constitute vibration, the number of these motions within a given time representing a given intensity. Any modification of the number of these to-and-fro motions within a given time, therefore, correspondingly modifies the intensity of the resulting vibratory impulse-wave, *the PASSIVE state of function (that during which cell-nutrition alone occurs) being represented by the lowest number of vibrations, the ACTIVE stage (during which the function is in full sway) by the highest number of vibrations compatible with normal health.*

Still, in accordance with my views, this applies to the impulses transmitted by the posterior pituitary body, since this organ, directly and through its extension in the cord, governs the passive stage of function and incites the cellular elements, both through the terminal vasomotors and the net-works distributed to the cells themselves, to higher activity when the active stage becomes necessary. Can we say the same of the independent hemispheres? This carries us back to the circulation of the brain, for the question involves another: *i.e.*, whether the cerebro-spinal functions, active and passive, are carried out in a manner similar to that of all other organs.

I am now able to state that they are, for *the neuroglia-fibrils of the substance of the brain and cord represent their blood-supply, just as the cellular capillary net-work of any other organ represents its blood-supply.*

Indeed, we must not overlook the fact that, while the neuroglia-fibrils representing the capillary supply of the cerebro-spinal substance are not supplied with vasomotor nerves, the peripheral vessels connected with the organ are, thus furnishing it with what might be described as an *extrinsic* supply. This extrinsic system would thus be represented by the pial vessels, which, as shown by Andriezen,⁵⁶ are supplied with vasomotor nerves. "We find," writes this investigator, "that it is possible to stain the vasomotor nerves with Golgi's method. Starting from the carotid and vertebral plexuses we can trace them no farther than the circle of Willis by anatomical dissection (using a lens). Do nerves accompany the cerebral arteries as they go off from the circle of Willis; and, if so, how far; and what is their ultimate distribution? Our observations on the kitten's brain show that bundles of nerve-fibers accompany the middle cerebral artery (the one specially chosen for our study) and its branches in the pia. These fibers run in tortuous and zigzag fashion, and in the finer pial branches they can be seen to form a very fine (non-anastomotic) plexus of fibrils lying between the outer and the muscular coats. From this *perimuscular* plexus terminal fibrils issue which, running a short distance along the muscular layer either longitudinally, transversely, or obliquely, end in small spherules: little ovoid bulb-like arrangements abutting against the muscular elements (cells). We have succeeded in tracing these terminals and their distribution to the finest pial cells, but no farther. The intracortical continuations of the pial vessels have constantly failed to give us the least evidence of this perimuscular plexus, which therefore—so far as our investigations go—we are compelled at present to imagine as *stopping with the pial branches*, and *not* continued along the intracortical vascular branches."⁵⁷ This evidence, added to the facts already outlined concerning the pericerebral vascular supply, seems to

⁵⁶ Andriezen: Brain, Winter, 1894.

⁵⁷ The word "not" is alone italicized by Dr. Andriezen.

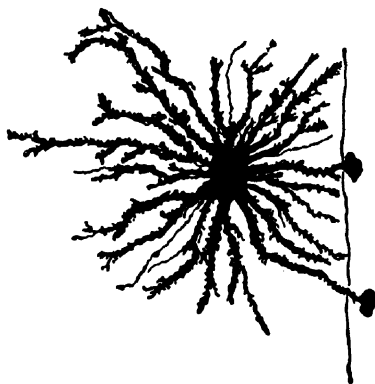
me plainly to indicate that *the cerebral circulation is governed, as is that of the arterioles of the body at large* (by the posterior pituitary body, as we shall see, pages 982 and 1259), *through the vasoconstrictor nerves of the pial vessels, which are terminals of the sympathetic system.*

This only furnishes us, however, the functional mechanism of the *passive* stage. In other words, the nervous energy developed owing to the presence of a given proportion of adrenoxidase (brought into contact with the myelin through the tonic vascular contraction insured by the general motor system) only causes the entire brain to create the nervous energy which, as we have seen, is essential to its own life. But how is the *active* stage incited in any one part of the cerebrum?

As is well known, groups of individual muscles may be caused to contract simultaneously, while some of the muscles which enter into the formation of these groups may be replaced by others. This is well exemplified by the mechanism of piano-playing: the index, thumb, and little finger, to form one chord; the annular and thumb to form the next, etc. Tracing this mechanism back to the structure which *incites* and *governs* the muscular adduction and abduction through which the keys are struck and released, we are brought back to a neuron. But how is the *neuron* incited to activity? In other words, how is the increased speed of blood through its myelin-lined dendrites, cell-body, and axon incited and governed? Can we ascribe this all-important function to the posterior pituitary body? We have seen that removal of the hemispheres did not prevent muscular action; a frog can swim, a pigeon fly, etc., and, indeed, continue to live a considerable time—months—if carefully fed, notwithstanding the absence of its hemispheres. This suggests that, while the posterior pituitary body either directly or indirectly incites and governs the functional activity of all organs, exception should be made of *the brain*, though it governs the circulation of this organ.

Still, the cellular elements of all organs are supplied with a net-work of terminal *nerves*, and it is through the intermediary in this net-work that its functional metabolism is governed by the posterior pituitary. How is the same function fulfilled in the hemispheres: *i.e.*, how are its cells, the

neurons, "incited and governed?" Are they also supplied with a net-work of fibrils which receives impulses from the posterior pituitary body? There is no evidence available to suggest that such is the case, and the functional relationship with the latter through the vasomotor supply of the pial vessels is the only link between the two organs that existing data permit us to accept. If, therefore, a regulative mechanism exists, it must be one connected with the vascular system, and so disposed as to enable it to govern the circulation through one or more neurons simultaneously. It must supply its own nervous energy, for we have seen that Andriezen found the vasomotor



nerves to distinctly terminate upon the muscular coats of the pial vessels; indeed, it must be as autonomous an organ as is the neuron itself.

Such an organ we have, it seems to me, in the neuroglia-cell shown in the above illustration, which Andriezen has named the "protoplasmic neuroglia-cell," and describes as follows⁵⁸: "The protoplasmic glia-cell has a distinct cell-body, which is irregularly oval, frequently pyriform. Its various protoplasmic processes are of moderate length; they exhibit *great variations of caliber*, some being stout and coarse and others exceedingly fine. These processes are also *dendritic*: a thing never seen in the stellate cells. A most striking feature is the *shaggy*

⁵⁸ Andriezen: *British Medical Journal*, July 29, 1893.

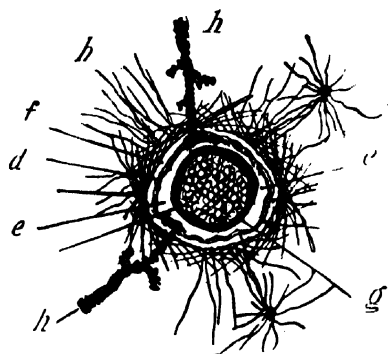
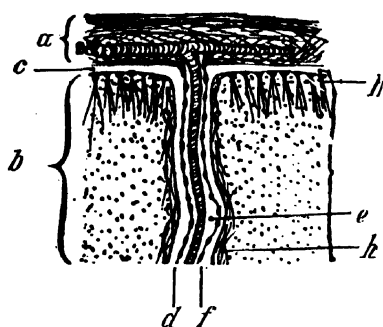
granular contour, as if a fine moss constituted the protoplasmic processes. . . . Further, by one or more of their *coarser* processes the protoplasmic cells are attached to the perivascular sheaths. The figure [on the opposite page] shows the cell with two such vascular processes, each *attached to the vessel* by a conical disk-like expansion ('foot')."

These characteristics of this cell speak clearly in favor of my view that neuroglia-cells and fibrils are channels for blood. Bearing directly upon the question in point, however, is the fact that this cell, as indicated by its gemmules and its dendritic appearance, must be supplied with myelin. The association of this myelin with the blood-plasma in transit at this point—*i.e.*, so close to the blood-vessel—seems suggestive, for, if the illustration is closely examined, dendrites are not alone found around the cell, but also fibrils, which start from various parts of these dendrites. That these protoplasmic neuroglia-cells are directly connected with the blood-vessels so as to admit plasma is demonstrated by the fact that they also take part in the engorgement of neuroglia structures that follow poisoning. "The bodies of the *mossy* neuroglia-cells," writes Berkley, alluding to the effects of ricin poisoning, "are larger than normal, rounded, sometimes globular in outline, and the tentacles are thickened and knotty. There are general evidences that these structures of the *lymphatic* system are undergoing modifications of a pathological nature." I have already stated that this "lymph" was, according to my view, its next o' kin: *i.e.*, *blood-plasma*.

Referring to the paper from which I have just quoted, Andriezen remarks⁵⁹: "We also stated at the time that the evidence of staining with Golgi's method shows us a system of lymph-spaces surrounding the cell-body and its branches. Careful and fresh observation confirm us in this opinion, viz.: that there is an *exceedingly fine system of canaliculi and lymph-spaces* surrounding the body, and dendritic processes of the protoplasmic glia-cell, and directly continuous with the perivascular lymph-spaces." If the annexed sketches *by Andriezen* are now examined and *interpreted from my standpoint*, addi-

⁵⁹ Andriezen: *Brain*, Winter, 1894.

tional testimony in favor of my conception of the whole mechanism of brain-function will appear. Indeed, the *canaliculi* are evidently the openings into the neuroglia-fibrils. But these microscopical channels, which are often one-sixth the size of a blood-corpuscle, would soon be blocked were the latter allowed to reach them. There is interposed between them, therefore, a lymphatic membrane, similar to the one which, as we have seen, forms the lymph-space from which veins start. Here, however, a double purpose is served, as shown in the sketch. It forms two cavities: the one surrounds the blood-vessel, and

• *Fig. 1.**Fig. 2.*

RELATIONSHIP OF THE VASCULAR AND LYMPH CHANNELS IN THE BRAIN. (Andriezen.)

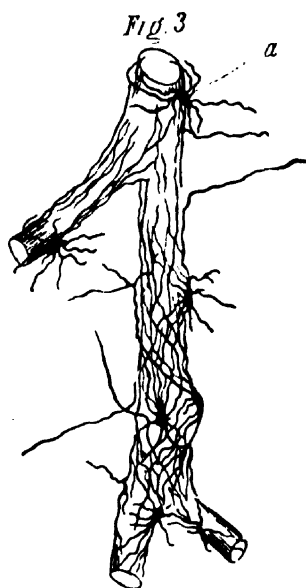
a, Pia-arachnoid. *b*, Brain-substance. *c*, Epicerebral space. *d*, Adventitial sheath. *e*, Intra-adventitial space. *f*, Extra-adventitial space.

(According to my view, these are all blood-channels: The blood arrives in pial artery (*g*), and escapes through the walls of the latter into the "intra-adventitial" space (*e*). Part of the plasma of this blood passes through sheath *d* into the "extra-adventitial" space (*f*) and enters neuroglia-fibers and cells (*h*, *h*, *h*), and then passes into the apical dendrites of neurons; the rest of the plasma and all corpuscles return to the veins by way of the "intra-adventitial" space at *e*.—*S.*)

represents the channel connected with the venous system, to which all corpuscles return; the other, or external, space receives only the blood-plasma which has passed through the membrane. The latter, being mainly composed of endothelial plates, is therefore phagocytic and bactericidal, and thus admits into the neuroglia canaliculi not only plasma relieved of all its

cellular elements, but also asepticiized adrenoxidase-laden plasma. The outside of a vessel covered with a neuroglia-ridden sheath is shown in Fig. 3.

The two kinds of neuroglia-cells may be seen to take part in the formation of the external net-work of fibrils in the illustration on page 586. It is here, it seems to me, that the governing attribute of the "protoplasmic neuroglia-cell" shows itself, as suggested by the dendritic appearance of its exten-



BLOOD-VESSEL OF THE HUMAN BRAIN, SHOWING SEVERAL NEUROGLIA FIBER-CELLS SURROUNDING IT AND FORMING A FELT-WORK (PERIVASCULAR SYSTEM). (*Andriezen.*)

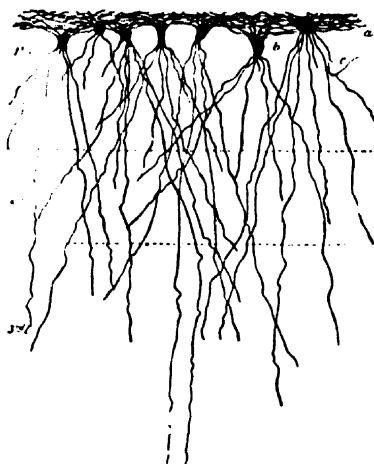
a, An encircling cell. *b*, Perpendicular neuroglia-fiber entering the sheath at right angles from a distant (extrinsic) cell.

sions. Indeed, Ranvier has been led to conclude that the other variety of neuroglia (stellate) cell is not much more than a mass of aggregated fibrils in transit, the latter passing through them without forming part of the cellular structure. Still, as it contains a nucleus, it may possess a regulative action. The larger cell, however, imposes itself as an organ of a very active kind—capable probably of playing in the brain the part that the vagus plays in various organs: *i.e.*, to incite

active function and govern it in the neurons with which it is connected, either directly or through the intermediary of other neurons. The connection with the latter would not be established by continuous fibers, but through their end-bulbs, the axonal of the one to the dendritic of the other, etc., in order to allow of the transmission of *vibratory* impulses. Referring to these larger "protoplasmic" ganglia cells, Andriezen writes: "They occur abundantly throughout the gray matter, in all the layers of the cortex, but are rare in the white substance." Indeed, according to my views, the latter is a mass of axis-cylinders coming from the upper strata, and surrounded by their myelin, wherein energy increases with distance: a true "avalanche"—using Pflüger's expression—of nervous force toward the lower cerebral structures.

The predominating function of both varieties of neuroglia-cell asserts itself, however, when the characteristics of the cortical layers are reviewed. The first, or molecular, layer contains but few nerve-cells, according to Andriezen. Its proximity to the pial vessels normally suggests that, if glia-cells are intermediaries between these vessels and the brain-substance's circulation, they should occur in large quantities in this region. "Its outermost, or superficial, region is formed of a system of neuroglia fiber-cells," says Andriezen, and by means of the annexed illustration, among others, he emphasizes the varied directions and the length their extensions may assume. But if the illustration on page 586 is examined, the manner in which these cells (according to my interpretation) are supplied with plasma may be easily understood. As shown therein, the pial vessel dips into the brain-substance, surrounded by its lymphatic membrane in such a manner, we have seen, as to form two spaces, the internal of which is for the blood and corpuseles to be returned by the veins to the general circulation; the other, or external space, being that in which the plasma for the neuroglia-cells passes after penetrating the lymphatic membrane, in order to reach the neuroglia-fibrils. This affords a supply to both kinds of cells, which are seen to line the plasma-containing space. That both are intimately connected with the circulation appears to me beyond doubt; that the mossy, or protoplasmic, cell is endowed

with some function other than as a mere distributing center is as likely; that this function should be to regulate the circulation in the neurons, or groups of neurons with which it is connected (as shown by the effects of poisons upon all structures thus connected), is strongly suggested by the fact that, while the need of such a regulative system is evident, there is no discernible or known organ or system of organs, directly connected with the pial blood-vessels, other than these cells to which this important function could be ascribed. The following conclusions, therefore, seem to me warranted:—



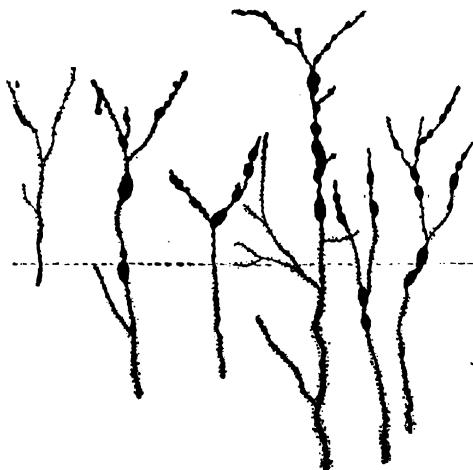
SEVEN CAUDATE NEUROGLIA FIBER-CELLS FROM THE HUMAN BRAIN-CORTEX (FIRST LAYER). (Andriezen.)

a, Tangential fiber-system. *b*, Cell-bodies. *c*, Descending fiber-system. The dotted line shows the limit between the first and second and the second and third layers.

The neuroglia-cells are the intermediaries between the general circulation and the capillary system (neuroglia-fibrils) of the brain-substance. The smooth stellate cell seems only to serve for the equable distribution of the blood-plasma to the neurons, while the mossy, or protoplasmic, cell presents the attributes of an organ to which the function of inciting a group of neurons to action by activating its blood-supply and of governing the quantity of nervous energy produced in these neurons can be ascribed.

Judging from the admirable histological work of Andriezen

and Berkley, the engorgement caused by poisons affects the three upper layers of the cortex most markedly. The bead-like swellings of the first-layer dendrites are well shown in the annexed illustration, the lesions being those found in alcoholic insanity. The second layer and third layer are represented by the plate opposite page 550, reproduced from Berkley's article, ricin poisoning, as previously stated, having been the cause of the cerebral engorgement. The cells of the last, or fourth (polymorphous), layer are not shown, but the fact that



TERMINAL TUFTS AND ENDINGS OF THE PROTOPLASMIC APICAL PROCESSES IN THE FIRST LAYER (HUMAN BRAIN-CORTEX).

(Andriezen.)

Showing bead-like and monilliform swellings, coalescence of fine miliary granules in place, and loss of fine granulation in the most affected parts. The dotted line marks the limit between the first and second layers. Alcoholic insanity.

Marchi found that the ependymal neuroglia-cells sent a central extension to the optic thalamus, where it divided and became attached to the blood-vessels, shows that the circulatory mechanism I have described applies to the entire cerebro-spinal system. Briefly, *the cerebro-spinal system is built up of neurons supplied with adrenoxidase-laden blood-plasma through the intermediary of protoplasmic neuroglia-cells, which regulate the volume of this fluid admitted into the neurons and, thereby, their functional activity.*

THE POSTERIOR PITUITARY BODY AS THE SOMATIC CENTER OF THE NERVOUS SYSTEM.

Howell,⁶⁰ in the course of experiments which led him to conclude that "the infundibular lobe of the hypophysis (the posterior pituitary) is, in all probability, not a rudimentary organ, but a structure that has some important physiological activity," found, as I have already stated, that "the extracts of the glandular lobe (the anterior pituitary) have little or no perceptible effect when injected alone. Extracts of the small infundibular lobe, on the contrary, have a distinct and remarkable effect upon the heart-rate and blood pressure, an effect which resembles, in some respects, and differs, in others, from that shown by suprarenal extracts."

We have seen in our previous analysis of these observations that the symptoms produced were those of suprarenal over-activity, and that the extract acted as did adrenal extract; the heart-beat was "not only slowed, but considerably augmented in force," says Howell, "as shown by tracings taken with a Hürthle manometer," etc. When both vagi were cut or a little atropine was given, the slowing of the heart was less marked. The result of vagal section is evident. As to the atropine, it prevented the slowing because, when added to the pituitary extract, it modifies its action, by inhibiting the functions of the adrenals as it does those of other glands. But an interesting query imposes itself in this connection: The extract having at first stimulated the activity of the adrenals, how did the latter, through the increased oxidizing substance, bring about increased vagal action? The answer is easily reached: the posterior pituitary being also increasingly supplied with oxidizing substance, its activity is likewise increased. This emphasizes an important feature: *i.e.*, that *the posterior pituitary is functionally stimulated, as is any other organ, by the oxidizing substance in the blood passing through it.* Indeed, the nerve-fibers which Berkley found to accompany the arteries suggest the presence of a functional arrangement similar to that of any organ, while

⁶⁰ Howell: "Transactions of Congress of American Physicians and Surgeons," vol. iv, p. 83, 1897.

the presence of so many neuroglia-cells at the apex—*i.e.*, where the posterior pituitary meets the infundibulum—indicates that the neurons which they supply are the seat of marked functional activity.

The feature brought out by Howell's experiments, however, is that the posterior lobe (including the *pars intermedia* as recently shown by Herring^{60a}) contains an active agency. This harmonizes with my views, since, as we have seen, the anterior lobe is, to a certain degree, passive in that it is stimulated to an inordinate degree only when toxics are present in the blood, while its normal activity is sustained by the secretion of the thyroid gland. Though the purpose of both organs is similar, therefore,—the conversion of chemical energy into nervous energy,—the manner in which this is done is not similar. Indeed, in the posterior lobe, the exciting agency is, as just stated, precisely as it is in any organ: *i.e.*, oxygen. The posterior pituitary must, therefore, become physiologically active through the same chemico-physical process that prevails elsewhere in the body.

Indeed, we have seen that the posterior lobe is, in reality, but an aggregate of neurons—and a precious aggregate it must be, enshrouded, as it is, in a bony cradle and resting on a pillow of blood, to preserve it against shocks or traumatisms! That, like all neurons, this aggregate depends mainly upon a phosphorus-containing ground-substance has been shown. I will recall that Cyon,⁶¹ in the course of a large number of experiments (since confirmed by Masay, see pages 983 to 989), observed that: "1. Any, even slight, pressure upon the hypophysis (*i.e.*, both organs) immediately gives rise to a sudden variation of blood-pressure and to a notable reduction in the beats of the heart, the strength of which is at the same time considerably increased. 2. Electrical stimulation of the hypophysis, even with extremely weak currents, produces exactly the same phenomena as does mechanical pressure, but in a much more intense manner. 3. Extract of hypophysis, injected into the veins of an animal, produces upon the heart and upon blood-pressure effects that are analogous to those caused by electrical and

^{60a} Herring: Quarterly Journ. of Exper. Physiol., vol. 1, p. 281, 1908.

⁶¹ De Cyon: Archives de Physiologie, July, 1898.

mechanical stimulation of this organ." I have pointed out that this pituitary extract does not prove the existence of a secretion at all, and that its action was due to the presence in the organ—as in all sympathetic structures, of chromaffine, *i.e.*, of adrenal substance. Indeed, Oliver and Schäfer in 1895 found that pituitary extract could be boiled without destroying its action—a property which a ferment such as the adrenal principle possesses alone. This added to the chromaffine and adrenalin reactions and the fact that the effects of pituitary extract are precisely those of adrenal extract shows the fallaciousness of the secretion doctrine. Conversely the facts reviewed the presence of phosphorus, noted by Rossbach, and the effects of direct stimulation, plainly show that *the posterior pituitary, being mainly composed of neurons and their protoplasmic extensions, is the seat of reactions similar to those that prevail in other nerve centers.*

The intrinsic processes upon which the physiological functions of neurons and nerves depend seem to me to be represented in the foregoing pages, but I have still to account for the "stormy processes in the nerve-fiber" to which Barker refers: *i.e.*, the exacerbations through which *passive* functions become *active*. Can we attribute these to the cells in the several centers? "Notwithstanding almost infinite minor variations in form," says Professor Barker, "the neurons in the most different parts of the nervous system present surprisingly similar general external morphological characteristics." We have seen, by the details furnished by the histological studies of Berkley, that such is not the case with the neurons in the posterior pituitary. Indeed, there are in this organ *ten* cells, exclusive of four of the neuroglia type that differ in morphological characteristics, each of which receives from Berkley a separate description. Not only do all the axons of the cells in this lobe point upward, but the diversity of cellular shapes is beautifully illustrated in the plate opposite page 594, a transverse vertical section of the infundibular region.

We have seen that above the infundibulum—*i.e.*, in the structures of the third ventricle—he found "varieties of ependymal neuroglia-cells, previously supposed to have entirely disappeared from the central nervous system," etc., and which

were thought to be confined to "reptiles, amphibia, and fishes." The physiological rôle I have ascribed to neuroglia-cells and fibers further emphasizes the importance of these structures and of the marked nutritional activity of which they are the seat. As a complement of this I showed that Andriezen traced a direct nervous connection in all classes of vertebrates between the "posterior lobe of the pituitary," on the one hand, and "the olfactory center" and the "bulbo-spinal centers," on the other.

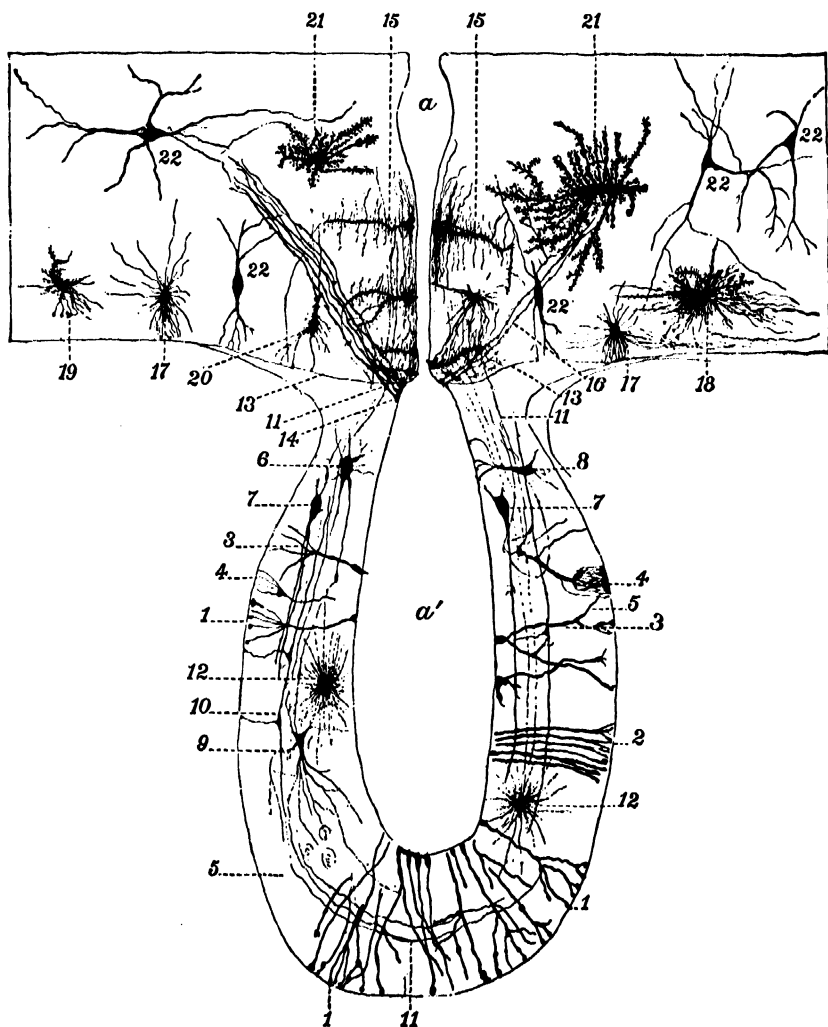
When these facts and others reviewed are placed side by side with the adduced evidence (1) that the middle brain is the seat of a nervous mechanism through which highly differen-

TRANSVERSE VERTICAL SECTION OF THE INFUNDIBULAR REGION.

a, Lumen of ventricle. *a'*, Lumen of infundibulum. 1, Primary forms of ependymal neuroglia, the processes extending from a cell-like body at the edge of the ventricular cavity to the subpial limit. 2, Coarser and less ramified variety of ependymal cell. 3, Coarser ependymal cells, branching within the inner half of the infundibular wall. 4, Portions of ependymal cells with tufted subpial branchings. 5, Unstained nerve-cells. 6, Pyramidal cells with long, fine processes. 8, Transversely lying cells of small size with knobbed extremities. 9, Pyramidal cells with large numbers of apical processes. 10, Probable axis-cylinder extension of pyramidal cells with thickenings, and rectangular extensions to the subpial limit. 11, Nerve-fibers passing from the infundibular wall into the tissues along the border of the ventricle. 12, Burr-like cells of the infundibular wall. 13, Line of the floor of the brain. 14, Long-rayed ependymal cells of the juncture of the ventricular and infundibular cavities. 15, 15, Fir-tree ependymal cells of various sizes and forms lining the border of the ventricle. A few of them are seen to have rounded knobs adjusted against the pial limit of the basis cerebri. 16, Neuroglia cell approximating the short-rayed type of Golgi. 17, 17, Sustentacular glia-cells of the inferior border of the tuber cinereum. 18, 19, Glia-cells with numerous long and stout hairy processes from the bodies, and thicker projections, probably transition forms between the sustentacular cells and cells of later development. 20, Probable nerve-cell resembling some of the glia-cells. 21, 21, Large mossy cells situated at some distance from the ventricular border. 22, 22, Nerve-cells of different forms. (*Berkley.*)

tiated afferent impulses meet with response, and (2) that the structures to which Berkley and Andriezen refer are contained precisely in the central gray matter which Foster considers as "perhaps in point of origin the oldest part of the brain" and which "seems to serve chiefly as a bed for the development of the nuclei of the cranial nerves," it seems clear to me that the posterior pituitary body is a *general center in which active functions are incited and governed in response to afferent impulses.*

A neuron, we have seen, presents the attributes of other organs; that the analogy includes the functional limits of these



SEMIDIAGRAMMATIC TRANSVERSE VERTICAL
SECTION OF THE INFUNDIBULAR REGION
OF THE BRAIN. [Barkley.]

[Brain.]

organs is very probable. Under these circumstances and taking the digestive system as example, a group of neurons constituting the origin of a nerve would be able automatically to continue its *passive* functions between meals. But just as the onset of digestion, the active functional state of the stomach, involves an increase of the volume of blood supplied to its muscular and secretory elements, through vasodilator impulses, so would a nerve-center, when required to assume the active phase of its functions receive more blood (adrenoxidase-laden plasma) through arterial vascular elements governed by the posterior pituitary.

Professor Foster's reference to the central gray matter as a bed "for the development of the nuclei of the cranial nerves" suggests that the posterior pituitary might possibly supply energy for all cranial nerves. The complex origins and connections of the optic nerve would, under these conditions, convert the posterior pituitary into a source of energy, pure and simple, for general distribution. Ample evidence to this effect is submitted in the second volume.

This does not apply to the anterior lobe, however, although its *pars intermedia* governs the adrenals. Berkley says, of the anterior pituitary: "No nerve-cells are to be found in the substance of the organ, and all nerves belonging to it appear to be derived from branches of the carotid plexus." This indicates that nervous energy supplied by this organ to the adrenal system, while produced through the intermediary of the layer of sensitive cells in the partition between the two lobes (see page 960 for its description), is due to a *stimulating* influence other than that which prevails in the posterior lobe. In other words, while the iodine in organic combination in the thyroid secretion is the *normal* stimulus of the sensitive cell-layer,—and one of the many stimuli to which it responds,—the posterior lobe is made up of many types of neurons which depend upon the lecithin formed between their protoplasmic partitions for their functional activity.

The organs differ markedly and significantly in one respect, therefore: *i.e.*, in the fact that, while the whole of the anterior lobe is devoted to the one purpose of energizing the suprarenal center, the posterior is an aggregate of many cen-

ters. This indicates, it seems to me, that if the organ were a general source of energy for the whole bed of cranial nerves, irrespective of the individuality and purpose of each nerve, it would have been similar in general construction to its mate, the anterior lobe. That it tends to suggest that each group of neurons in the posterior pituitary body is a highly specialized center for a single class of nerves. Indeed, this is experimentally, though indirectly, sustained by Andreizen's researches. He could not have traced a direct nervous connection with the olfactory bulb and with the cerebro-spinal axis had the organ been a center for the production of energy intended to be diffused promiscuously in the central gray matter.

Again, the connection between the posterior lobe and the nervous system cannot be limited to the cranial nerves, since we have seen how intimate is the functional relationship in which afferent impulses obtain, between the middle brain and the entire motor system. Were the cranial nerves alone involved, the skeletal muscles would have to be omitted from the list of structures under the organ's control. As we have seen, removal of the middle brain abolishes all "bodily movements," as Foster puts it, "carried out by means of co-ordinate motor impulses, influenced, arranged, and governed by coincident sensory or afferent impulses."

Yet, how can the posterior lobe influence organs with which it has no anatomical connection? Thus, the most prominent motor paths, the pyramidal tracts, arise, in the cortex, from the upper two-thirds of the central convolutions, pass down behind the knee of the internal capsule, and then penetrate the middle third of the pes cerebri, then the pons and the medulla, and finally pass down the cord. Where is the connection with the posterior pituitary? When the tracts "emerge from the pons," says Edinger,⁶² "their fibers form two large bundles in the ventral portion of the medulla,"—i.e., in the regions of the middle brain,—where, as we have seen, not only all nerves endowed entirely or in part with motor properties—the second, third, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh, and twelfth pairs—are represented either by their nuclei

⁶² Edinger: *Loc. cit.*

or by communicating roots, but also where *all nerves acquire certain vasoconstrictor, i.e., sympathetic properties.*

It becomes a question as to the manner in which the cerebrum is itself functionally governed, in so far as its somatic functions are concerned. In the light of the foregoing facts we are brought to the eminently logical conclusion that, in order to insure perfect co-ordination of the functional activity in all organs, a single structure is entrusted by Nature with this all-important rôle, *i.e., the posterior pituitary. The cerebrum, as the organ of Mind, differs in no way from other organs, from my viewpoint: its circulation is also governed by the pituitary body during its active and passive state: wake and sleep.* I have previously referred to the fact that the medulla is only a transmitting center: a general station to which impulses from various directions arrive by the cord from below, by the commissures from the encephalic structures, and establish junctions with the several paths with which they are related. "The encephalon is a very complicated system of large and small continents of gray or central nervous substance," says Professor Duval, "communicating one with another and with the medulla by numerous commissures."

We have seen how absolutely independent of motor functions the hemispheres are, though volitional attributes enable them to *utilize* the motor system. Indeed, the experimental evidence adduced on this score is incontrovertible. But the same distinguished physiologist says: "The nerve-cells of the cord form in this organ a continuous central gray mass, extending from one extremity of the organ to the other. But, if the anatomist locates the superior limit of the cord on a level with the occipito-atloidian articulation, for the physiologist the cord extends into the interior of the cranium; it reaches to the aqueduct of Sylvius (the true origin of the motor oculi communis and patheticus) and even on a level with the third ventricle—the gray substance of the walls of this ventricle." We have seen that he also referred to its reaching up to the *sella turcica*. That it is *within* this bony structure that the main center of this vast mechanism—with its extensions and terminals, including the vasomotor fibers—lies, has been sufficiently emphasized. I feel, therefore, that I have good

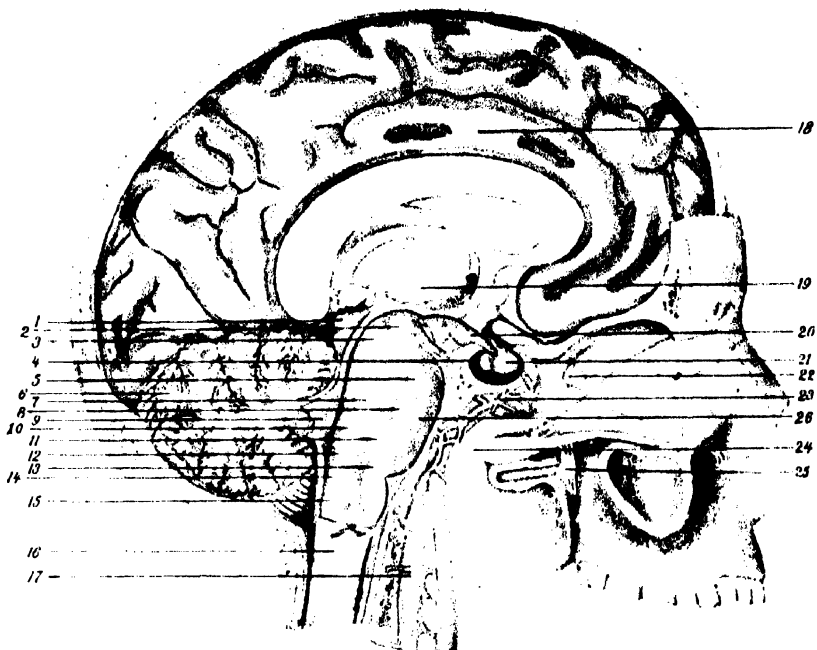
ground for the previously-mentioned postulate that the posterior pituitary is a chief center from which arise excito-motor impulses now thought to originate in the bulb.

The relationship that exists between the cranial nerves and the posterior pituitary body now becomes apparent. Not only does it seem as if the motor properties either *in toto* or in part owed their functional impulses to this body, but those which regulate its functional blood-supply also. Again, as *all* organs require functional impulses and blood, and inasmuch as these impulses and the blood must be incited and governed, *all* organs must be functionally dominated by the posterior pituitary body. Indeed, all the data that I have presented in this work tend to show that *the posterior pituitary body is a dominant center of the organism; it influences the functional activity of all organs, through the intermediary of the subsidiary centers located in the bulb and spinal cord.* The scope of these functions is defined in the sixteenth chapter.

The anatomical relations of the posterior pituitary are shown in the annexed plate which portrays the relationship between this organ, the floor of the third ventricle, the medulla, the pons, and the cord—all of which are continuous.

THE POSTERIOR PITUITARY AS THE SENSORIUM COMMUNE.

From all the data submitted and the normal functional association embodied in reflex phenomena manifested through various nerves—the vagus, for example—motor-efferent phenomena are the normal sequences of sensory-afferent impressions, and the two are necessarily linked. The pons Varolii, or at least its *gray ganglionic substance*, is now thought to originate motor impulses that are independent of mental processes and to be the seat of *instinctive* acts. "It is, indeed, to the pons," says Professor Duval, "that, in a general way, we appear authorized to ascribe the most important rôle in great emotional expressions: laughing, weeping, the cry of pain; in a word, involuntary manifestations. It is in this sense that the term *sensorium commune* applied to the pons should be understood. Indeed, if, as was done by Vulpian, the *corpora striata*, the *optica thalami*, the *tubercula quadrigemina*, and the *cerebellum* are



THE POSTERIOR PITUITARY BODY AS GENERAL CENTER OF THE NERVOUS SYSTEM. [*Binjous*]

Showing Continuation from the Posterior Pituitary Body, of the Infundibulum, the Floor of the Third Ventricle, the Medulla Oblongata, and the Cord.

1, Corpora Quadrigemina. 2, Motor Oculi. 3, Patheticus. 4, Posterior Pituitary Body. 5, Motor Branch of Fifth. 6, Cerebellum. 7, Abducens. 8, Trigemini. 9, Fourth Ventricle. 10, Glosso-pharyngeus. 11, Facial. 12, Pneumogastrio [*Vagus*]. 13, Auditory. 14, Hypoglossal. 15, Spinal Accessory. 16, Spinal Cord. 17, Superior Cervical Ganglion. 18, Left Hemisphere. 19, Third Ventricle. 20, Infundibulum. 21, Anterior Pituitary Body. 22, Optic Nerve. 23, Carotid Plexus. 24, Cavernous Ganglion. 25, Spheno-palatine Ganglion. 26, Pons Varoli.

successively removed, the animal still shows, by characteristic agitations and *plaintive* cries, the pain it experiences when submitted to strong external excitations: *i.e.*, when its leg is squeezed with pincers or a bare nerve is excited. If the pons itself and the upper part of the medulla are now destroyed, the animal at once ceases to respond by similar cries and agitations." . . . "An animal that has lost its pons has therefore lost a center for the perception of sensitive impressions." The gray ganglionic substance of the pons is, we have seen, a part of the central gray matter which begins in the posterior pituitary body: a fact which suggests that the latter may be the seat of functions now ascribed to this part of the pons.

Indeed, these instinctive involuntary acts are dominant in the entire phylogenetic scale even in vertebrates devoid of skull or brain: the amphioxus, for example, down to which Andriezen traced the structures which ultimately become the pituitary bodies. It is difficult to conceive of an *inciting* and *governing* efferent impulse from the posterior pituitary without an afferent impulse conveying to it the needs of the organ to be incited to activity and governed. Duval refers to weeping, for instance; tears, we have seen, are brought on by increased circulation and stimulation of the cellular elements of the lacrymal glands; what is this but functional activity enhanced by impulses to the posterior pituitary—if my previous conclusions are at all warranted?

True, we are dealing primarily with a mental phenomenon, but this only proves that afferent impulses may reach the posterior pituitary from the cortex of the hemispheres as they can from any organ. Nor is the act an instinctive one; but this fact also affords supporting testimony, since it tends to show that the organ is not only influenced by impressions of a purely reflex kind, or connected merely with organic life, but also by the highest form of nervous action: *i.e.*, mentality. What better evidence can we have of this than the violent cardiac action; the trembling; the involuntary excretion of urine, of feces, of sweat; or even the sudden arrest of the heart, all of which phenomena may attend intense fear, and all due to loss of control by the posterior pituitary, under the violence of the mental impulses over . . . muscular tissue: cardiac, skele-

tal, cystic, intestinal, and sudorific? To this list I may add loss of control over all vasoconstrictors, since we have relaxation of the larger internal vascular trunks, central engorgement, in virtue of the principle—"vessels supplied with a muscular coat and capillaries are mutually antagonistic in contraction and dilation"—submitted in the earlier chapters and the mechanism of which we can now understand. Both antagonistic conditions are expressed in another symptom of fear: *i.e.*, intense pallor, the lividity of Asiatic cholera and, indeed, of the moribund. Truly instinctive, however, is the sudden cry or scream brought on by unexpected pain: evidently the result of an impulse to the posterior pituitary, since we again have a series of muscular actions of the chest, glottis, etc., which are necessary for the cry. Laughing, sneezing, coughing, and other kindred acts are all manifestations of motor activity; and so is vomiting the result of afferent and efferent vagal impulses, again with muscular structures as the mechanical factors and the posterior pituitary as inciting and governing organ.

And a striking proof of this is furnished by the fact that these manifestations of activity not only prevail in a frog deprived of its hemispheres, but that, if the animal is kept alive and in good health, signs suggestive of intelligence appear. "For days or even weeks after the operation," says Professor Foster, "there may be no signs whatever of the working of any volition; but, after the lapse of months, movements, previously absent, of such a character as to suggest that they ought to be called voluntary, may make their appearance. . . . Even in their most complete development such movements do not negate the view that the frog, in the absence of the cerebral hemispheres, is wanting in what we ordinarily call a 'will.'" Nor need they, for these so-called involuntary, instinctive acts are dominant even in vertebrates devoid of skull or brain: the amphioxus, for example, down to which Andriezen traced the structures which ultimately become the pituitary bodies.

That the posterior pituitary is a *discerning* organ, and one, at that, capable of simultaneously subserving many functions, seems very probable. Totally independent of the brain, *though its servant when need be*, it appears to me as the undoubted seat of the many centers—*i.e.*, for cardiac action, respira-

tion, vasomotor action, sneezing, coughing, etc.—that have been located in the medulla oblongata. True, local disease or traumatism point to the “bulbar” areas concerned as “centers.” But if the bulb is given the rôle which I believe it to fulfill,—*i.e.*, that of a secondary or rather subsidiary *consociating* organ,—it will become apparent that any lesion capable of blocking the multitude of afferent and efferent impulses that traverse it at all times and which represent the aggregate of the organisms inciting and governing energy must necessarily compromise life or the functions of an organ to which the blocked nerves are distributed.

I have expressed the belief that there are but two general subdivisions of the nervous system, and that both of these have the posterior pituitary body as their general center. This view has not only been sustained by the analysis of the functions of the various organs, but it seems to me fully to coincide with established facts.

As Regards Efferent (Motor) Impulses.—It has been experimentally determined that all fibers that originate from roots in the *anterior* portion of the cord are *efferent*: *i.e.*, transmit motor impulses from the cord to the periphery. Section of these fibers causes: in muscles, paralysis; in glands, cessation of secretion; in vessels, dilation.

Interpreted from my standpoint, these morbid phenomena are accounted for as follows: As the *active* functional state of any organ is brought on, we have seen, by strictodilation of its arterioles, *i.e.*, constriction of their vasa vasorum (that attending the *passive* functional state), section of the nerve transmitting the constrictive impulses brings on the opposite of active function,—*i.e.*, paralysis,—or, if distributed to a gland, arrest of secretion. Although the same impulses serve to *incite* and *govern* the cellular activity of the organ, paralysis, muscular or glandular, is not due to the loss of these two functional attributes, since section of vagal efferent nerves, which only incite and govern the active functional state beyond tonic contraction, does not cause paralysis. The immediate cause of the latter is slowing of the blood-stream: *i.e.*, reduction of the supply of oxidizing substance. The cellular elements lose their mechanical energy and can no longer be incited to action and governed. The

mechanical energy being due to the adrenoxidase present, it is traceable through the adrenal system to the *anterior pituitary body*, while the inciting and governing influence, being of cerebro-spinal origin through the anterior root severed, is traceable to the *posterior pituitary body*. That it is of central origin is shown by the fact that removal of the pituitary is followed by general vasodilation.

Control experiments are represented by the well-known facts that stimulation of an anterior root causes vasoconstriction and increased functional activity, and, if sufficiently strong, convulsive movements of muscles. The latter, as we have repeatedly seen, are due to excessive oxidation of the muscular elements—complemental testimony to the effect that inadequate oxidation is a primary source of paralysis or at least of functional inhibition.

I have previously shown that the bulbar vasomotor center and the cranial nerves that possessed motor properties occupied the same medullary region: the *upper*. As general motor nerves possess vasomotor properties, the reason for this is obvious. Again, we have seen that the cranial nerves which acquire motor properties by anastomosis were grouped in the *lower* portion of the medulla. The entire organ thus becomes a conductor for general motor impulses, whether transmitted by the cord (as indicated by the general vasodilation incident upon medullary section) or by cranial nerves.

Although this aggregate of motor areas in the medulla represents but radiating paths from a common center, the posterior pituitary lobe, present conceptions as to their distribution—whether to the extremities, the thorax, the cranial nerves, etc.—or their anatomical relations with the hemispheres—the cerebellum, etc.—are in no way modified. All we need to bear in mind, and as will be shown later, the sympathetic system is not an autonomous system of nerves, and that it is a subdivision of the general motor system originating, like all motor nerves, from the cord, while its impulses emanate from the pituitary.

Summarized, these facts—which will be supplemented by evidence in the second volume—suggest that, *while the medulla oblongata is an important consociating organ, its centers receive*

impulses from, and are controlled and co-ordinated by, the posterior pituitary body.

Unlike the anterior lobe, which governs and sustains oxidation and metabolism through the adrenals, however, the posterior lobe is not necessary to life, since it is but a co-ordinating structure.

As Regards Afferent (Sensory) Impulses.—It has likewise been experimentally ascertained that all fibers that originate from roots in the posterior portion of the cord are *afferent*: *i.e.*, transmit sensory impulses from the periphery toward the cord. Section of these roots is followed by loss of sensation.

Interpreted from my standpoint, sensory impressions are similarly transmitted from all parts of the organism, and the one general sensory system supplies the needs of all. The nature of the impulse being governed by the specific cellular characteristics of the peripheral structures which receive the impressions, whether related to a special sense, general sensibility, variations of functional activity, etc., they all reach the posterior pituitary. That such is the case is suggested by the fact that, while frogs deprived of the hemispheres exhibit typical signs of continued co-ordination and sensation, removal of the bulb then causes them no longer to show these signs. This does not exclude the functions of subsidiary centers,—*i.e.*, reflex centers, ganglia, etc.,—which probably serve as accumulators of energy, and act in lieu of the posterior pituitary body unless the peripheral stimulation exceed their potential as to the efferent energy actively used. The law of generalization of Pflüger,—*i.e.*, propagation of (reflex) impulses to the medulla under excessive excitation,—which, according to my view, applies to the posterior pituitary, typifies the maximum effect produced under such conditions, and further demonstrates the connection between the periphery and the latter organ.

Control experiments are represented by the familiar results of stimulation of the dorsal roots, which causes augmentation of reflex activities and of conscious sensations. The reflex inhibition of functional activity of certain organs I have ascribed to excessive stimulation: in accord, therefore, with foregoing facts. This affords the complementary concordance

required to place my conception of the functions involved on a solid foundation.

All these data suggest a postulate, the importance of which must be emphasized: *i.e.*, the identity of the posterior pituitary body as the center upon which all emotions, shock, etc., react, and as the organ which initiates the phenomena that attend the impressions thus produced.

That this organ is directly or indirectly connected with the cerebrum in all phenomena pertaining to intelligence, reason, and will, precisely as its motor functions—other than the purely automatic ones—may be dominated by these higher manifestations of nervous activity, need hardly be emphasized. “Sensory” in its broad sense, from my viewpoint, and refers to impressions received by all end-organs endowed with sensation, as previously stated. Whether these first reach the eye, the ear, the cutaneous surface, the gustatory papillæ, the olfactory area, etc., or be due to traumatism, surgical procedures, an abnormal mental state, such as attends fear, grief, or other emotions, etc., we are always dealing with molecular jarring of the posterior pituitary body: harmless when slight, pathogenic when sufficiently intense, but fatal when a certain limit is reached. Precisely as the current passed through the region by the Weber brothers inhibited the heart, so can fright, intense pleasure, or shock prove fatal by inhibiting the heart, but primarily by *jarring the posterior pituitary body*—or, speaking more correctly, by inducing excessive molecular vibration of its elements.

The maximum effect of shock thus becomes an arrest of nervous impulses through which function is sustained *via* the cerebro-spinal axis. This may well be illustrated by the description given by Professor Stewart of the “various phenomena which are grouped together under the name of shock” as exemplified by section of the cord. “When the spinal cord of a dog is divided,—*e.g.*, in the dorsal region,—all power—all vitality, one might almost say—seems to be forever gone from the portion of the body below the level of the section. The legs hang limp and useless. Pinching or tickling them calls forth no reflex movements. The vasomotor tone is destroyed, and the vessels gorged with blood. The urine accumulates,

overfills the paralyzed bladder, and continually dribbles away from it. The sphincter of the anus has lost its tone, and the faeces escape involuntarily." I hardly need to emphasize the fact that we have here a summary of all the phenomena which attend loss of functional activity: of those, at least, I ascribe to the posterior pituitary body.

But this experimental section of the cord was also chosen as an example of the wonderful resources of nature when life's functions are to be preserved. "If we were to continue our observations only for a short time, a few hours or days," continues the author, "we should be apt to appraise at a very low value the functions of that part of the cord which still remains in connection with the paralyzed extremities. But these symptoms are essentially temporary. They are the results of shock; they are not true 'deficiency' phenomena. And if we wait for a time, we shall find that this torpor of the lower dorsal and lumbar cord is far from giving a true picture of its normal state; that, cut off, as it is, from the influence of the brain, it is still endowed with marvelous powers. If we wait long enough, we shall see that, although voluntary motion never returns, reflex movements of the hind-limbs, complex and co-ordinated to a high degree, are readily induced. Vasomotor tone comes back. The functions of defecation and micturition are normally performed. Erection of the penis and ejaculation of the semen take place in a dog. A man with complete paralysis below the loins and destitute of all sensation in the paralyzed region has been known to become a father (Brachet). Pregnancy carried on to labor at full term has been observed in a bitch whose cord was completely divided above the lumbar enlargement."

How can the return of functions—so far unexplained by physiologists—be accounted for? The foregoing data suggest that the pituitary should be the organ "shocked" by the operation. Moreover, removal of this organ, except after its gradual destruction by disease, produces identical effects. Indeed, the resumption by the lower and dorsal cord of its normal functions would not occur if the path from the pituitary to the adrenals had also been severed. As Goltz and Ewald have shown, animals deprived of their cord from the bulb down cannot keep

warm, and even die of cold; but Ott found that this did not happen when the section was made below the fifth dorsal. As this is immediately below the region where the pituitaro-adrenal nerves leave the cord to enter the sympathetic chain and thence pass on to the adrenals, these results find their ready explanation: As soon as the posterior pituitary had recovered from the shock, it resumed its influence on the adrenals, the secretion of which, as previously shown, endows the hæmoglobin with its oxygenizing constituent. Metabolism—the life process—being resumed in the severed segment of the spinal cord, its normal functions returned.

It seems extraordinary to connect the adrenals—as I did in 1903 in the present work—with fright, anger, traumatic shock, etc.; and yet the recent experimental work of Cannon and de la Paz,⁶³ in the Harvard laboratories of physiology, has demonstrated that under the influence of such emotions in the cat the inferior vena cava contains an excess of secretion. Cannon and Hoskins^{63a} also state in this connection: “The similarity between surgical shock and the condition of an animal after removal of the adrenal glands suggests that possibly in surgical shock the injury to large nerve trunks may discharge the adrenal glands to such a degree that they are unable to continue their normal functioning.”

If to all this be added the fact that the manner in which violent emotions, fright, trauma, shock, etc., provoke various diseases, exophthalmic goiter, railway spine, and concussion, for instance, it seems probable that *the posterior pituitary body, as the most highly organized aggregate of somatic nerve-centers, is the organ upon which all shocks—physical, i.e., cerebral or traumatic—react.*

Illustrative also of the rôle of shock, physical and mental, in the production of disease is acromegaly. Fully 20 per cent. of these cases are due to some form of accident, often falls upon the head. Its syndrome, better than any other disease, shows, from my viewpoint, the relationship between the pituitary and the body at large. Hence its presence at the end of the present chapter.

⁶³ Cannon and de la Paz: *American Journal of Physiology*, April 1, 1911.

^{63a} Cannon and Hoskins: *Ibid.*, April and December, 1911.

ACROMEGALY: PIERRE MARIE'S DISEASE, AND GIGANTISM.

The first question that imposes itself in this connection is whether the pathogenesis of this disease of the pituitary body must be based upon the prevailing belief that this organ is a secreting gland or, as I believe, upon its identity as a co-ordinating center which includes, among its functions, that of governing the secretory activity of the adrenals and thyroid apparatus.

I have already urged that the prevailing opinion that the pituitary is a secreting gland has so far remained unproven, while every item of evidence brought in favor of this view can be shown to be questionable as such. The main argument in its favor is that extracts of its posterior lobe can produce vasomotor phenomena; but this fact loses its value in the presence of Wiesel's⁶⁴ demonstration that this lobe is rich in chromaffin substance, *i.e.*, in adrenal principle. That under these conditions its extracts should give rise to the same phenomena as the latter is plain. To enumerate these phenomena is to rehearse all those that were credited to the secretion of the adrenals in the second chapter by the many investigators cited therein. Thus, Mairet and Bosc⁶⁵ found in 1896 that subcutaneous injections of pituitary extract caused a rise of temperature which lasted a couple of hours. An intravenous dose produced marked myosis, slowing of the respiration, powerful cardiac beats, and hyperthermia as main signs, the animals recovering, however. Schäfer and Vincent⁶⁶ then found that pituitary substance raised the blood-pressure, and that this substance when applied to mucous membrane caused blanching, as is the case when a solution of adrenalin is applied. They also noted that in small mammals it caused, in toxic doses, paralytic symptoms which *they* also consider analogous to those caused by adrenal extracts. According to Jas. Barr,⁶⁷ pituitary extract actively produces arteriosclerosis, and it is also known to produce glycosuria. Finally, Hallion and Carrion, studying its therapeutic action, found that pituitary extracts "always produced their effects by

⁶⁴ Wiesel: *International Clinics*, vol. II, 15th series, 1905.

⁶⁵ Mairet and Bosc: *Arch. de physiol.*, p. 600, 1896.

⁶⁶ Schäfer and Vincent: *Jour. of Physiol.*, vol. XXV, p. 87, 1899.

⁶⁷ Barr: *Lancet*, Nov. 13, 1899.

raising the arterial tension." In other words, it awakens all the typical phenomena, physiological and pathological, to which the adrenal product gives rise.

Twelve other general facts, covering a wide scope of research in the domain of various branches, submitted on page 510, also indicate that the pituitary is not a secreting organ.

Again, if the pituitary body were the source of an internal secretion its removal, as has been repeatedly done in recent years by Hochenegg, Cushing, and others for tumors, should prove harmful if not fatal, as is the case when the thyroid apparatus or the adrenals, which we *know* to be the source of internal secretions, are removed. But such is not the case. If, on the other hand, the pituitary is considered, with me, as a co-ordinating center supplied with subsidiary centers in the bulb, which centers could normally assume its functions gradually as the chief center is being destroyed, we can readily understand how a degenerated and useless pituitary can be removed with impunity.

Twenty-six years have elapsed since Pierre Marie identified acromegaly with the pituitary, and it must be admitted that the secretory theory has served but little if anything to elucidate its pathogenesis. Indeed, notwithstanding the painstaking labors of many distinguished observers, George Dock⁶⁸ could but write of it recently (1911): "Acromegaly is closely associated with disease of the pituitary body, but the alterations reported by various observers have been interpreted so differently that it is still uncertain just what the true relation is." The semeiology of the disease and its pathology have been raised quite to the high level of diseases that have had the benefit of centuries' analysis; but the relation between the seat of lesion and the clearly defined external phenomena of the disease still belong to the domain of conjecture. Will my interpretation of the functions of the pituitary body prove more fruitful in results? All that is claimed for it is that it offers a field for new lines of thought.

PATHOGENESIS AND SYMPTOMATOLOGY.—Tamburini⁶⁹ has shown, after an analysis of twenty-four cases in which autopsies

⁶⁸ Dock: Musser and Kelly: "Practical Treatment," p. 853, 1911.

⁶⁹ Tamburini: Riv. Sper. di Fren., p. 559, 1894, and p. 414, 1895.

had been made, that "in all *typical* cases of acromegaly a growth of the pituitary prevailed, but that there was, at first, hypertrophy of the gland, *with exaggeration of its functions*, and, later on, *abolition of these functions*," a view in which Harlow Brooks,⁷⁰ after a painstaking study of the whole subject, concurs. These and other facts I will submit below have suggested the advisability of dividing the disease into two stages, the first representing the ascending period of the disease in the sense of exaggerated nutrition, terming it the *sthenic* stage, and to add thereto another stage representing the period of decline, as was done in other diseases of the ductless glands, namely, the *asthenic* stage. This will make it possible to identify the meaning of each symptom, and also, perhaps, to suggest more effective remedial measures than those now employed.

The characteristic phenomena of acromegaly have naturally established it as a disease of nutrition, as foundation for the many theories that have been advanced to explain its pathogenesis. To account for its symptoms, therefore, through organs such as the thyroid and adrenals, to which I have attributed such leading functions in oxidation and nutrition, must *a priori* seem, to say the least, reasonable. Again, the identity of the pituitary body as the starting point of the disease has been demonstrated by Marie and many other observers since. If, therefore, exaggeration of function is followed by abolition of function, another established fact, we have seen, we are brought to the logical conclusion that the diseased pituitary first excites the thyroid and adrenals, which, as I have shown, provoke hyperthyroidia and exophthalmic goiter, and also hyperadrenia, and that it subsequently depresses these same organs, bringing on, to a more or less marked degree, the opposite states: hypothyroidia, myxœdema, and Addison's disease or its milder prototype hypoadrenia. Interpreted from this viewpoint, then, the disease might be defined as follows:—

Acromegaly is a disease of nutrition, due to any condition, hyperplasia, neoplasm, etc., of, or any pressure upon, the pituitary body, capable of primarily exciting abnormally this organ, and then of progressively annulling its functions, and also, therefore, those of the organs it controls, viz., the adrenals and thyroid

⁷⁰ Harlow Brooks: Arch. of Neurol. and Psychopath., vol. 1, No. 4, 1898.

apparatus, whose combined secretions sustain tissue oxidation, metabolism, and nutrition. Its symptoms are, during the first stage: excessive tissue growth, merged with those of hyperthyroidia and hyperadrenia, and, during the second stage, with those of hypothyroidia and hypoadrenia.

No reference is made here to the other functions of the pituitary in order to restrict the morbid process to its main general cause.

The *sthenic* stage is replete with clinical evidence of the participation of the thyroid apparatus in excessive development of the body. There are several cases of acromegaly on record which, by showing in an exaggerated manner the involvement of the pituitary,—to the point of bringing on all the prominent signs of exophthalmic goiter,—clearly indicate the participation of the thyroid even in those cases in which such prominent phenomena do not appear. Thus, Lediard⁷¹ exhibited a case before the Clinical Society of London, in which the accompanying goiter was sufficiently large to require operation. Neal and Smyth⁷² also witnessed a case in which a parenchymatous goiter was present. Sometimes swelling of the neck, which develops into a goiter, is the first symptom observed, as in a case reported by Grove.⁷³ In these cases, which but exemplify many others on record, the goiter might, however, occur as an independent condition. But in many instances the full syndrome of exophthalmic goiter is present. Lancereaux⁷⁴ reported 5 such cases, and Murray⁷⁵ 2 out of 4 cases of acromegaly he had witnessed. Exophthalmus, tremor of the hands, and glycosuria were prominent features. Hinsdale,⁷⁶ in fact, found exophthalmus in 23 out of 130 reported cases—evidence of the frequency with which the major symptoms of exophthalmic goiter are present, and of the important factor the thyroid apparatus must represent in the pathogenesis of acromegaly.

As to the adrenals, we must not lose sight of the fact that we are dealing with the *sthenic* stage of the disease, *i.e.*, that in which both the thyroid apparatus and the adrenals are rendered

⁷¹ Lediard: Brit. Med. Jour., April 4, 1903.

⁷² Neal and Smyth: London Lancet, July, 1898.

⁷³ Grove: Bulletin Johns Hopkins Hosp., Sept., 1910.

⁷⁴ Lancereaux: Semaine médicale, June 24, 1896.

⁷⁵ Murray: Edinburgh Medical Journal, p. 170, 1897.

⁷⁶ Hinsdale: "Acromegaly," p. 23, 1898.



CASE OF ACROMEGALY, EXOPHTHALMIC GOITER,
PHTHISIS, AND GLYCOSURIA. [*Murray.*]

overactive by the irritated pituitary. Here, therefore, the connection is with excessive activity of the adrenals, such as adrenal hypernephromas furnish. Now, Owen Richards⁷⁷ describes such a case in a girl of 7 years, "who was as tall as a person of 20." Tileston and Wolbach,⁷⁸ referring to this type of cases, state that "they are obese and abnormally large for their age, a child of 5 years having the size and general appearance of a boy of 16 (Linser's case). Pigmentation of the skin may occur, but the color is more like that of a brunette than like the bronzing seen in Addison's disease. The intellect is dull and the disposition sullen. Appetite and sometimes thirst are increased, and vomiting is likely to be an obstinate feature" . . . As these phenomena occur as the result of an excess of an adrenal tissue, however, the body growth might only occur solely as an effect of such a surplus of adrenal secreting tissue; but that normal adrenals under stress—as they are in acromegaly—are capable of producing it, is well shown by the additional statement of Tileston and Wolbach's, that "in three instances (Otto,⁷⁹ Crecchio,⁸⁰ Marchand⁸¹) premature development has been associated with simple hyperplasia of the adrenal glands."

We thus have functionally overactive the two organs known to stimulate growth by their secretions: the adrenals, we have just seen, and the thyroid, as illustrated by its influence on body growth in the treatment of cretinism; and if, as Meige wrote: "Gigantism is the acromegaly of the growing period, while acromegaly is the gigantism of the period of completed development," these two organs, beyond doubt, account for the morbid growths. When to this we add the recognized fact that the thyroid apparatus influences calcium metabolism, we have all the factors necessary to trace the most characteristic phenomenon of the disease: the progressive enlargement of the bones and soft tissues, to its source. Marie restricted his conception of the disease to enlargement of the extremities (hence, *ἄκρον*, extremity, and *μέγας*, large), but, besides these, the bones of the skull, face, arms, and legs, the spinal column, scapulæ,

⁷⁷ Richards: Guy's Hospital Reports, vol. lix, p. 217, 1905.

⁷⁸ Tileston and Wolbach: Amer. Jour. Med. Sci., June, 1908.

⁷⁹ Otto: "Path. Anat.," p. 139, 1816. Cited by Tileston and Wolbach, *Ibid.*

⁸⁰ Crecchio: Wien. med. Presse, N. 30, p. 783. Cited by Tileston and Wolbach, *Ibid.*

⁸¹ Marchand: Beitr. zur Wissensch. Med., B. 1, 1891. Cited by Tileston and Wolbach, *Ibid.*

clavicles, and the ribs are also caused to grow, increasing the stature in the young and building upon giants, but causing deformities (projection anteriorly and posteriorly of the thoracic cage—of which the double hump of Punch or Punchinello is the type—in some) in adults. The soft tissues over the entire body are no less overnourished; the enormous hands and feet, the hypertrophied muscles, which, notwithstanding their great bulk, are weak, and the hypertrophied heart, scalp, face, lips, tongue, penis, etc., bear witness to this fact.

Side by side with this morbid growth we witness, more or less marked, the other phenomena of thyro-adrenal activity. There is abnormal demand for food; indeed, bulimia is considered by Hinsdale⁸² as “one of the characteristic signs of acromegaly”—a fact which points to exaggerated metabolism. Thirst is also marked in some cases “out of all proportion to even the extraordinary size of the subjects,” says the same writer, a symptom which he connects “with the glycosuria present in many cases.” But here, also, we are dealing with a prominent symptom of exophthalmic goiter, and also of adrenal over-activity, since, as shown by Blum, Herter, Croftan, and others, injections of adrenalin produce it. So marked, in fact, is the connection between acromegaly and exophthalmic goiter and glycosuria that it has attracted attention. Lorand,⁸³ for instance, observed, independently of my views, that there was an intimate relationship between these disorders; that similar conditions: fevers, traumatisms, shock, etc., brought all three on; that polyuria, polydipsia, polyphagia were also met in all. In all three also more or less pronounced swelling of the thyroid occurred, having himself noted it in diabetes. Launois writes in this connection: “Whether we adopt the view of Loeb, involving pressure changes, or that of Sajous, relative to nervous irritation [transmitted to the thyroid, adrenals, etc.], however, the presence of an intermediary is further required for the production of glycosuria. According to some, this intermediary factor is the pancreas; in the opinion of Gilbert and his followers, it is the liver which, under these conditions, becomes functionally overactive; according to Sajous, it is the adrenals, to

⁸² Hinsdale: *Loc. cit.*, p. 27.

⁸³ Lorand: *La Presse médicale*, Sept. 19, 1903.

which he traced nerves from the pituitary." Here, again, my views harmonize those of others: the adrenal secretion, by enhancing general metabolism, increases the functional activity of the pancreas and thereby the production of amylpsin; the hepatic glycogen is then converted by this ferment into glucose at an abnormal rate, producing glycaemia and glycosuria. Hence, it is by exciting the adrenals that the pituitary in acromegaly causes glycosuria. The circulatory phenomena include, we have seen, tachycardia where other signs of exophthalmic goiter prevailed. Others have noted a "paradoxical acceleration of the pulse." The "frequent and copious sweating," the tremors, the cramps, paræsthesias, tingling, shooting pains, due to circulatory disturbances in the neurons, sensory endings, etc.; dyspnoea, the anomalies of tastes, the tinnitus aurium, are all symptoms of acromegaly common to exophthalmic goiter. Both often give a history of rheumatic pains and occasionally symptoms of unbalanced mind, especially delusions of fear or maniacal excitement. Conversely, in both diseases the patient may lapse into a condition of melancholia. In both, also, are witnessed the brand of adrenal overactivity, a swarthy, or dirty yellowish-brown hue of the skin, more marked in some parts than others.

Passing to the *asthenic* stage, the connection with myxœdema as to failure of thyroid functions, and with Addison's disease as to adrenal insufficiency, is quite as clearly defined. "Myxœdema may form part of the hypophysial syndrome," writes Launois. "From the observation of Norman Dalton⁸⁴ to that of Sainton and Rathery⁸⁵ a large number of cases have been reported which support the view that this combination can occur."

The functional relationship between the pituitary and the thyroid is well shown by the case of myxœdema reported by Sainton and Rathery, just referred to, in which the pituitary had been destroyed by a malignant growth, while the thyroid, adrenals, and ovaries were atrophied. Here the period of growth of the tumor had evidently caused excessive activity—hyperæmia—of the other organs and finally their functional destruction by atrophy, with myxœdema as a result. Other cases

⁸⁴ Dalton: *Lancet*, Nov. 6, 1897.

⁸⁵ Sainton and Rathery: *Société médicale des Hôpitaux*, May, 1898.

of the latter in which the pituitary was destroyed have been reported.

Strikingly suggestive in this connection is a case of myxœdema reported by Adami,⁸⁶ in which there was cancer of the pituitary, while the thyroid was normal. This shows plainly that it was to the absence of the impulses from the pituitary that the hypothyroidia was due. When, therefore, in acromegaly, the pituitary loses, by gradual degeneration, its power to excite the thyroid, hypothyroidia occurs, while the general tissue hypertrophy remains over from the sthenic period. The general signs of exophthalmic goiter are then gradually replaced by those of myxœdema, though the symptom-complex of the latter is somewhat obscured by the physical changes remaining over from the first stage; still, cases of acromegaly have been reported in which the myxœdematous symptoms were sufficiently marked to warrant the conclusion that the two diseases were associated. Lyman Greene,⁸⁷ Auerbach,⁸⁸ and others have reported such cases.

The phenomena of hypothyroidia and its progressive form myxœdema both include, we have seen, hypothermia. "A no less singular manifestation," writes Launois,⁸⁹ referring to acromegaly, "is lowering of the internal temperature, which, in a patient of Bartels, remained for weeks at a time between 34° and 36° C. (93 $\frac{1}{5}$ ° and 96 $\frac{4}{5}$ ° F.) without the supervention of any sign of collapse. The same phenomenon has been witnessed by Petrina. In a case reported by Götzl and Erdheim,⁹⁰ the temperature fluctuated for three weeks between 35° and 36° C. (95° and 96 $\frac{4}{5}$ ° F.), later falling to 33° C. (91 $\frac{2}{5}$ ° F.) It would be rather difficult at the present time to explain the origin of such disturbances," continues Launois; "we shall merely point out their similarity to the phenomena observed in myxœdema, in which disorder the temperature often fluctuates between 33° and 35° C. (92 $\frac{4}{10}$ ° to 95° F.) and sometimes even falls below these figures." This symptom is no paradox when interpreted from my viewpoint, since, as I have shown, the pituitary governs

⁸⁶ Adami: *Trans. Cong. of Amer. Phys. and Surg.*, p. 114, 1897.

⁸⁷ Lyman Greene: *N. Y. Med. Jour.*, Oct. 21, 1905.

⁸⁸ Auerbach: *Wiener klin. Woch.*, Feb. 10, 1907.

⁸⁹ Launois: *Monthly Cyclopaedia and Medical Bulletin*, Jan. and March, 1911.

⁹⁰ Götzl and Erdheim: *Zeitschr. f. Heilkunde*, vol. xxvi; *Intern. Med.*, p. 372, 1905.

the thyroid apparatus, while the adrenals, in turn, sustain tissue oxidation, and therefore the body heat.

"Unusual sensitiveness to cold," mental and physical torpor, and marked asthenia are also typical signs of hypothyroidia and hypoadrenia approximating Addison's disease. Facial œdema and even the moon face of hypothyroidal infantilism may be witnessed, as in Glaser's case,⁹¹ though the deformities of the face, the prognathism, the projecting brows, mainly due to the osseous overgrowth of the sthenic stage, tend to conceal the myxœdematous signs in this region. There is often marked accumulation of fat, giving no œdematous pitting, and presenting the resistance to pressure as in myxœdema. This can evidently be of pituitaral origin; in a case reported by Madelung,⁹² for example, a shot in the infundibulum was followed by marked obesity. Indeed, Fröhlich and Launois have elaborated syndromes, since sustained by numerous cases, in which adipose overgrowth is directly connected with neoplasms of the pituitary. There is good ground for the belief also that Dercum's disease, *adiposis dolorosa*, is primarily due to disorders of the pituitary. That thyroid gland is used as a remedy for obesity is known to every one; that obesity should occur when the thyroid apparatus is rendered deficient through inhibition of its center—the pituitary—by disease is self-evident.

Dilated veins, as in the infantilism of hypothyroidia, are commonly observed in acromegaly, though these may occur as a remnant of the sthenic stage. Suppression of sexual desire and impotence and amenorrhœa, rheumatic pains, neuralgia, are also common, as in hypothyroidia. A painful form has been identified which "may assume," says Launois, "the rheumatoid type when it becomes localized in a certain group of joints"—a sentence which reminds us vividly of the labors of Léopold-Lévi and de Rothschild, referred to under hypothyroidia. As in myxœdema we may also meet with various forms of delirium, delusions of persecution, mystery, and the manic depressive psychoses, and even with epileptic seizures. These are mainly due, as I have shown, to the accumulation of toxic wastes in the blood incident upon the inhibition of the antitoxic functions—

⁹¹ Glaser: *Virchow's Archiv*, B. cxvii, p. 389, 1890.

⁹² Madelung: *Langenbeck's Archiv für klin. Chir.*, lxxvii, p. 1066, 1904.

a result, in turn, of the deficient activity of the three organs which, from my viewpoint, take an active part in the process, the pituitary, the thyroid apparatus, and the adrenals.

The implication of the adrenals in acromegaly has been referred to in connection with the sthenic stage—that of overgrowth. In the asthenic stage we witness the effects of their functional decadence. “Small freckles are frequent,” writes Pirie,⁹³ referring to a personal case; “patches of a yellowish bronzing occur on the face, the chest, and the insides of the thighs. (Motaïs describes a bronzing such as occurs in Addison’s disease.) . . . The patient suffers from a brownish seborrhœa, especially troublesome in the scalp. The hair is thick and coarse. Palpitation and fainting fits occur often. Dyspnœa and asthmatic-like attacks occur, during which the patient has to sit up in bed and fight for her breath,” attesting to marked insufficiency of the adrenals in the respiratory process. Harlow Brooks⁹⁴ also writes, “macroscopically, the skin in these areas is considerably thickened; the surface is rough and often fissured. A general brownish pigmentation is present in the average case, which, at times, strongly resembles that found in Addison’s disease.” But the signs of myxœdema are again apparent in the remark by Pirie, that the skin of the eyelids was “thickened and puffy,” there being also increased lachrymation and “a colloid secretion between the eyelids”—the typical “watery eyes” of myxœdema.

The symptoms that belong to the domain of the pituitary proper, *i.e.*, those which are not brought about through the agency of the thyroid and adrenals, are the ophthalmic disorders, including progressive amblyopia, amaurosis, hemianopsia, etc., the result in turn of pressure by the enlarged pituitary upon the optic tracts, the chiasm, optic nerves, etc. That the headache, sometimes extremely severe, from which these patients may suffer is also due to pressure is probable, though we must remember that it may also occur during the early or sthenic stage of the disease, and may then be due to increased intracranial tension.

PATHOLOGY.—The prevailing view, at the present time, is that of Marie, which ascribes the disease to a secretion of the

⁹³ Pirie: London Lancet, Oct. 5, 1901.

⁹⁴ Brooks: Archives of Neurology and Psychopathology, vol. 1, No. 4.

gland. We have now seen, however, that there is considerable evidence to the contrary, *i.e.*, in favor of my own view, that it is through the adrenals and thyroid mainly that the characteristic phenomena of the disease are produced. Marie's original idea that the disease is due to disease of the pituitary is strongly sustained by my views, however, though still a matter of doubt among a few observers.

An important feature of the whole question is the predilection of the pituitary body for sarcoma, though, as suggested by Tamburini, Benda, Mendel, and others, many of these sarcoma-like tumors, on close histological differentiation by means of appropriate stains, proved to be examples of hyperplasia or adenoma, in which the destructive process does not proceed with as great rapidity unless the adenoma be malignant, which is frequently the case. This accounts for the fact that in many cases, particularly in women, the progress of the disease seems to be rapid, the asthenic stage, that characterized by hypothyroidia and hypoadrenia, coming on before the typical acromegalic changes and overgrowths have had time to advance materially. This probably corresponds with Parona's figures, which indicate that sarcoma or adenosarcoma is present in 64.5 per cent. of all cases.

That adenoma of the pituitary frequently occurs without giving rise to signs of acromegaly, or in fact to any symptoms, has been shown by Lowenstein. But we must not overlook the fact that many faces among the multitudes show marked evidences of overactivity of the pituitary at a given time of their existence. I have had occasion to treat a young man 6 feet 2 inches tall, in whom the prominent orbits, nose, and chin clearly indicate temporary hyperactivity of the pituitary. The same phenomena, though far more marked as to facial deformities than in the preceding case, were also observed in an average-sized woman by Léopold-Lévi, who pointed her out to me at the Rothschild clinic in Paris.

That children's diseases are frequently the source of temporary hyperplasia of the anterior lobe of the pituitary, I have no doubt. This sustains the personal view, treated at length in the second volume, that this lobe and the *pars intermedia* are mainly concerned, as a sensory organ, with the defense of the organism at large against disease.

TREATMENT.—Launois, referring to the cases in which Hochenegg removed the pituitary, states that “the progressive retrogression of the manifestations of acromegaly witnessed after excision of hypophysial tumors affords an argument of the first importance in favor of the theory of glandular hypersecretion.” From my viewpoint, it affords a no less strong argument in favor of my view, since by removing the pituitary Hochenegg arrested the cause of the overstimulation of the thyroid apparatus and adrenals, to which the disease is due. Indeed, the latter view is the stronger, since the actual existence of a secretion from the pituitary is still a matter of conjecture, while the existence of the thyroparathyroid and adrenal secretions is beyond question.

The treatment of the disease has been necessarily restricted to symptomatic measures, and to the promiscuous use of organic preparations. The foregoing pages indicate that such should not be the case, and that, whatever use is made of the latter, they should always be carefully adjusted to the *stage* in which they are indicated. As stated by Dock,⁹⁵ “pituitary glands and extract have not produced definite improvement. The same may be said of thyroid treatment which has often appeared to make the symptoms worse.” It is self-evident that in cases in the sthenic stage with the hyperthyroidia approximating, if not actually reproducing, exophthalmic goiter, and the blood already replete with thyroid secretion, the addition of thyroid gland to it cannot but prove harmful. But in a case such as Sears’s,⁹⁶ in which the asthenic stage—which may appear early in women—was present, with signs of hypoadrenia, a puffy and mask-like face, dry and coarse hair, etc., with brown patches and asthenia denoting hypoadrenia, especially where, as the author specifies, “the thyroid could not be felt,” considerable benefit can be obtained under thyroid treatment. In the sthenic or first stage, especially where the signs of exophthalmic goiter are marked, the treatment for that disease (see page 229) is indicated. The use of coal-tar products, it includes, is known in fact to afford considerable relief of the most distressing symptom of acromegaly, intense headache. Acetanilid and antipyrin, and also aspirin, have been considerably used for this purpose.

⁹⁵ Dock: *Loc. cit.*, p. 854.

⁹⁶ Sears: *Boston Med. and Surg. Jour.*, July 2, 1896.

With respect to the therapeutic value of pituitary extract a case reported by Rolleston was greatly improved by pituitary and thyroid extracts combined. But the author observed that the superficial resemblance of acromegaly to myxœdema seemed to justify the administration of thyroid extract, pituitary extract alone having failed to effect any improvement. The patient neglecting the treatment, ultimately died, the autopsy revealing a sarcoma of the pituitary—a type of growth which rapidly brings on the asthenic stage.

As to the use of pituitary alone in the asthenic stage, it has been found of value in some cases as a palliative for headache,⁹⁷ but Rénon and Delille⁹⁸ found, in a woman who showed clear symptoms of hypothyroidia, that it aggravated the acromegalic signs, including the deformities of the face, hands, feet, etc. Yet, in similar cases, the simultaneous use of thyroid has proven of value. The solution of this enigma was furnished by Rolleston⁹⁹ when he said that “the apparent success obtained from the administration of the combined extracts was in reality due to the thyroid extract.” On the whole, all this indicates that, as soon as any sign of hypothyroidia or myxœdema appears, the treatment for the latter disease (see page 192) should be instituted.

In the light of the facts submitted under the heading of pathology, particularly those which refer to arrest of the morbid process, there is ground for the hope that appropriate remedies may further such a result. Until our hopes are fulfilled, however, operative measures, such as those introduced by Hochenegg in Europe and admirably developed by Cushing in this country (see his recent volume¹⁰⁰), should be resorted to where remedies do not check the lethal trend.

⁹⁷ See chapter xii, this volume; article “Pituitary Organotherapy.”

⁹⁸ Rénon and Delille: *Le Bulletin médical*, June 24, 1908.

⁹⁹ Rolleston: *Brit. Med. Jour.*, April 17, 1897.

¹⁰⁰ Cushing: “*The Pituitary Body and its Disorders*,” Philadelphia and London, 1913.

CHAPTER XI.

THE INTERNAL SECRETIONS AND THE LEUCOCYTES IN IMMUNITY AND FEVER.

THE ADRENAL SYSTEM AS THE FOUNDATION OF IMMUNITY.

To understand the *vis medicatrix naturæ*, i.e., nature's way of antagonizing disease, and learn how to enhance her resources when these fail has increasingly imposed itself as the goal for which we should strive. So concordant is the thought, in fact, with our highest aims as physicians and humanitarians that it may be said to have seen light at the very dawn of medicine, and to have grown apace with time. Indeed, twenty-three centuries ago Hippocrates¹ taught: "It is to the efforts of nature that the attentive and able physician looks for guidance." Galen² was no less affirmative when he wrote: "Nature having originally formed the body must, when disease assails it, restore health." Today, the most virile trend of modern thought is a corresponding principle, that conveyed by the term "immunity." Whether we seek to identify the nature of antibodies, the process through which they are caused to appear in the blood, or the manner in which they and the phagocytes oppose infection, we are but following the path opened by the father of medicine 400 years before the Christian era.

We have now learned through the painstaking labors of a host of investigators that our organism is supplied with autoprotective substances; but, so far, the identity of these substances has not been revealed by them. Even Ehrlich's theory has failed in this particular. His side-chain theory, notwithstanding the many collateral facts the labors devoted to it have brought out, has remained but a clever figment of imagination in so far as the side-chain feature itself is concerned—a pure assumption the truth of which he is yet to demonstrate, notwithstanding the many years it has been most carefully studied.

¹ Œuvres médicales d'Hippocrate, ed. Foës, II, p. 195, 1801.

² Galen: "Contra Julianum."

Nor have the sources of the various substances which take part in the immunizing process so far been identified. Ehrlich hypothetically attributes this rôle to the tissue-cell, but, even granting that this be so, we are only driven back—unless we remain with him within the field of conjecture—to the necessity of showing whence these cells obtain their immunizing bodies, his so-called receptors. This he has failed to do, along with all other investigators in the same direction, because, in my opinion, he and they have overlooked the one field which, experimentally and clinically, offers the only solid foundation for a profitable analysis of the question, that of the ductless glands. Brown-Séquard, Langlois, Abelous, Charlin, Albanese, Zucco, and many others, we have seen, have laid stress on the antitoxic functions of the adrenals, while Vassale, Gley, Fano, and Zanda, and many other investigators and clinicians have urged a similar rôle in respect to the thyroid and parathyroids. This applies equally well to the pituitary body, according to Marie, Guerrini, Gemelli, and others. We thus have a series of organs found *experimentally and clinically* to protect in some way the body against intoxication. Is it not logical to conclude that they claim attention as the more likely to furnish the factors for a solution of this all-important problem?

Prompted by these indications, I advanced the view in the first edition of the present work (1903) that the body was supplied with *an immunizing mechanism*. I showed that the adrenals and the thyroid were the sources of two substances regarded by pathologists as prominent agents in the immunizing process, but the source of which they had not identified, and that the secretory functions of these organs were governed by a center located in the pituitary body. I suggested, moreover, that it was probably by exciting this center that various familiar drugs, mercury, for instance, and certain toxins, tuberculin, Coley's toxins, and the like, produced their beneficial effects. The eight years that have elapsed since these views were advanced have served only to strengthen them.

The identity of this mechanism suggests itself in view of the details already submitted in the chapters upon the adrenals, the parathyroid apparatus, the pituitary body, and the

kidneys. But to facilitate the discussion of the subject, I will merely recall that, interpreted from my viewpoint, the functions of these organs, both physiological and defensive, are as follows:—

Adrenals.—These organs supply a secretion which, on reaching the lungs, absorbs the oxygen of the air and becomes a constituent of hæmoglobin—its albuminous constituent. It is, as such, taken up by the red corpuscles and secreted by these cells as droplets (the so-called “blood-platelets”) in all parts of the body, including the *blood-plasma* itself. The purpose of this albuminous hæmoglobin, which I have termed “adrenoxidase,” is to supply oxygen to the tissues and to the blood. Important in this connection, however, is that this adrenoxidase gives the reactions and presents other characteristics of a familiar agent in the classic immunizing process, the *immune body* or *amboceptor*.

The active participation of the adrenal secretion in the defensive function suggests itself when the connection between oxidation and fever is recalled. Adrenoxidase being the active agent in all oxidation processes, and being capable of raising the temperature, we have a clue to the identity of one of the most important of the symptoms we meet on all sides, and the actual nature of which has not, so far, been explained, namely, *fever*. Indeed, as stated by Lazarus Barlow²: “Even if we grant that fever is beneficial, we are completely ignorant of the manner in which it acts.”

We may speak of neurogenic fever caused by injury to the corpora striata; of aseptic fever due to crushed tissue; of infective fever caused by certain pathogenic organisms or their toxins, or of hyperthermia, and of the nature of the substances that are oxidized, but the identity of the oxidizing agent, the *deus ex machina* in all these types, has remained obscure. This is the feature of the problem which, from my viewpoint, the adrenal secretion, converted in the lungs into adrenoxidase, supplies.

Barlow writes, moreover: “Experiment seems strongly to support the view that hyperthermia has a curative action, and thence it is but a short step to considering fever as beneficial,

² Barlow: “General Pathology,” 2d ed., p. 435, 1904.

and as evidence of the setting in motion by the organism of one of its defensive mechanisms. And certainly in pneumonia, erysipelas, cerebrospinal meningitis, typhoid fever, the prognosis is better if the patient's temperature is moderately high than if it is definitely low." Now, we have seen by the labors of Albanese, Abelous and Langlois, Charrin, Oppenheim, and others that the adrenals also enhance the defensive power of the body, thus combining the production of fever with the beneficial action—which dates back to Hippocrates and has been defended by many of the most illustrious investigators of modern times—to which Barlow refers.

Thyroparathyroid Apparatus.—The thyroid gland and the parathyroid glandules, which constitute this apparatus, produce secretions which, on passing out of the lymphatics (into which they are secreted), enter the left subclavian vein, and become merged into a single substance. Passing then into the blood of the superior vena cava, this secretion is carried to the lungs, and on reaching the air-cells is taken up by the red corpuscles—along with the oxygenized adrenal secretion. A salient feature of the immunizing process appears in this connection, viz., the thyroparathyroid product is also secreted by the red corpuscles into the blood and tissues, and, by acting directly upon the phosphorus which the nuclei of all tissue-cells, pathogenic organisms, etc., contain, increases their inflammability, *i.e.*, their sensitiveness to oxidation. As such, it acts both as *opsonin* and *agglutinin*.

The thyroparathyroid secretion taking part in tissue oxidation with the adrenal product, it becomes also, logically, a normal participant in the production of fever. Now, this is so striking a feature of thyroid functions that the thyroid gland has been associated with the production of fever by Lorand and other authorities on the ductless glands. Lorand⁴ urges in this connection the various manifestations of the febrile state, elevation of the temperature and the sensation of heat observed in Graves's disease, due, as is well known, to excessive activity of the thyroid, and many other phenomena peculiar to the febrile state. "Both in Graves's disease and fever," he writes, "there is an augmentation of the processes

⁴ Lorand: *Lancet*, Nov. 9, 1907.

of oxidation." Again, as previously shown, thyroid feeding causes febrile phenomena, *i.e.*, a rise of temperature of several degrees, both in man and animals, as shown by the researches of Chantemesse and Marie, Ballet and Enriques, Bourneville, and others; it increases the intake of oxygen and the output of carbonic acid, the output of sodium chloride, phosphoric acid, etc. Finally, operative or morbid arrest of thyroid functions causes hypothermia.

Once more, and in keeping with Barlow's remarks concerning the beneficial influence of fever, do we find the thermogenic properties of the thyroid associated with marked defensive or immunizing activity. Besides the evidence to this effect I have already offered (see page 163) may be mentioned the protection it affords against toxic products of protein decomposition noted by Breisacher⁵—as far back as 1889, and by Blum,⁶ Galeotti, and Lindemann⁷—and others. The increased vulnerability of myxedematous subjects to infection, the rapidity with which thyroidectomized animals succumb to practically any infection that happens around are now familiar clinical facts. In his recent work, Swale Vincent^{7a} states that "it may be supposed that the function of the internal secretion is to prevent poisoning by the products of body metabolism or by infections from without." My opinion that the thyroparathyroid product is what Wright has termed "opsonin" has been sustained, we have seen, by the investigations of Marbé, Malvoz, Stepanoff, and others.

THE PITUITARY BODY AS THE SEAT OF THE IMMUNIZING CENTER.—Considered in connection with immunity only, the pituitary body contains, from my viewpoint, a center—the immunizing center—located in the pars intermedia (between the two lobes) and connected with the adrenals and the thyroparathyroid apparatus by nerves. Through these nerves the immunizing center governs the functional activity of these two sets of organs, and, therefore, the production of adrenoxidase (amboceptor) and of thyriodase (opsonin and agglutinin), besides general oxidation. As such, the immunizing center is also the heat of fever center, the febrile state indicating that one or

⁵ Breisacher: Arch. für Anat. u. Physiol. Supp., p. 509, 1889.

⁶ Blum: Archiv f. d. Ges. Physiol., p. 617, 1902.

⁷ Lindemann: Virchow's Archiv, p. 202, 1897.

^{7a} Swale Vincent: "Internal Secretions and the Ductless Glands," p. 353. London, 1913.

more poisons are present in the blood which this dual center is antagonizing through its militant agents, the thyroparathyroid apparatus and the adrenals—and also indirectly, as we shall see later, through the phagocytes.

To interpret this process intelligently, I will submit, as was done in the cases of the adrenals, the thyroparathyroid, and the pituitary, an outline of the main features of the evidence I have to offer, referring the reader to the second volume for a detail study of the whole question.

Of fundamental importance in this connection, is that

The pituitary body of all animals, from mollusks to man, contains a sensory organ which structurally resembles the nasal olfactory membrane.

Julin⁸ urged, in 1881, that in ascidians the subneural gland (conjoined to the nerve ganglion which I assimilate to the posterior or neural lobe) was the ancestor of the pituitary body of vertebrates. Lloyd Andriezen⁹ confirmed this view after a comprehensive study of the organ, from amphioxus to man. Personal work in the same line led to a similar conclusion. Now, at least as low down as mollusks there exists in the corresponding location a patch of epithelium, which Spengel has termed "the olfactory organ," and Ray Lankester¹⁰ the "osphradium." Unaware of the connection between this structure in ancestral forms and the pituitary, Peremeschko,¹¹ Müller,¹² and also Cadiat¹³ described a cleft between the two lobes of the latter organ, the walls of which they found to be lined with epithelium. The structure of this epithelium was only made clear, however, when the Golgi method was available. Gentès¹⁴ then found that it was merged in the partition (the *pars intermedia*) separating the two lobes, and that it contained elongated nerve-cells which sent their neuraxons into the posterior lobe, and thence to the base of the brain. According to Gentès, these cells recall exactly the sensory elements of the nasal olfactory membrane. Caselli

⁸ Julin: "Recherches sur l'organisme des ascides simples," Arch. de biol., II, pp. 59, 211, 1881.

⁹ Lloyd Andriezen: British Medical Journal, January 13, 1894.

¹⁰ Ray Lankester: Article Mollusca, in Encyclopædia Britannica, 9th ed., xvi, p. 636.

¹¹ Peremeschko: Virchow's Archiv, xxxviii, p. 329, 1867.

¹² Müller: Jenaische Zeit. f. Naturw., vii, p. 327, 1873.

¹³ Cadiat: Anatomie générale, cited by Guépin, Tribune méd., December 10, 1891.

¹⁴ Gentès: C. r. de la Soc. de biol., iv, p. 100, 1903.

also found sensory elements in the pituitary of higher animals, while Boeke¹⁵ and Gemelli¹⁶ discerned them in the pituitary of fishes. A personal distinctive study of this organ from the true olfactory apparatus has shown, moreover, that the former could be traced down to lower forms, gradually receding in importance until the patch of epithelium "supplied with a special nerve and ganglion," as Ray Lankester describes it, in mollusks is reached.

Suggestive in this connection, as a feature of the immunizing process, is that

In ancestral animals the "test organ" serves to test the purity of the sea water ingested by them.

Spengel's olfactory organ, Ray Lankester's osphradium, has for its purpose, according to zoölogists, to test the respiratory fluid. In amphioxus, the lowest of vertebrates, similar protection is afforded by what Willey¹⁷ describes as a "vestibule richly provided with sensitive cells," and by Andriezen as a "nervous organ" which "serves to test the quality of the water which passes over the respiratory organ."

That a corresponding autoprotective function exists in the higher animals, including man, is not only sustained by considerable evidence, but a solid foundation for the whole scheme is afforded by the fact that the blood of these higher animals is the physiological and qualitative homologue of sea water. Claude Bernard¹⁸ taught forty years ago that "the blood is an internal medium in which anatomical elements live as do fishes in water." René Quinton¹⁹ showed that our plasma was a fluid which chemically, in so far as the relative proportion of the various elements was concerned, corresponded with sea water. A. B. Macallum²⁰ also holds that both animal and vegetable protoplasm derive their relations to the elements sodium, potassium, calcium, and magnesium from the composition of sea water which obtained when all forms were unicellular. The labors of Bunge,²¹ Jacques Loeb,²²

¹⁵ Boeke: *Anat. Anz.*, xx, p. 17, 1902.

¹⁶ Gemelli: *Jour. de l'anat. et de la physiol.*, 42d year, No. 1, 1900.

¹⁷ Willey: "Amphioxus and the Ancestry of Vertebrates," p. 19, 1894.

¹⁸ Claude Bernard: "Leçons sur les propriétés des tissus vivants," pp. 55-58, 1866.

¹⁹ René Quinton: *Paris Correspondent, Lancet*, April 16, 1904.

²⁰ Macallum: *Trans. Canadian Institute*, p. 181, 1903-4.

²¹ Bunge: "Physiological and Pathological Chemistry," English translation by Starling, pp. 101, 102, 1902.

²² Loeb: *Pflüger's Archiv*, cvii, p. 252, 1905.

Matthews, Fisher, Overton,²³ and others have all contributed testimony to the solidity of this view.

Considered in the light of the anatomical connections of the pituitary with the thyroid and adrenals, and the functions I have ascribed to these organs, the conclusion seems warranted that

In the higher animals, including man, the "test organ" tests the purity of the qualitative homologue of sea water, the blood, for toxic substances and, where possible, causes destruction of these substances.

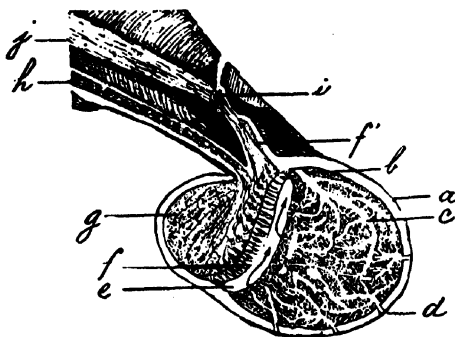


Fig. 1.—PITUITARY BODY, CONTAINING IMMUNIZING CENTER (semi-schematic). *a*, anterior lobe; *b*, arteries and, *d*, arterioles; *c*, course of blood diffused through sinusoidal capillaries of epithelium; *e*, cleft into which contents of blood-cells (colloid) and cellular detritus are driven, and whence they pass into lymphatics; *f*, sensory test organ (immunizing center) excited by colloid when the blood (and therefore the colloid) contains certain poisons; *g*, posterior pituitary containing origin of paths to adrenals and thyroid; *h*, tuber cinereum, showing secretory path to adrenals and thyroid; *i*, retro-optic nucleus which transmits, *j*, sympathetic vasoconstrictor nerves to various organs, including the thyroid.

We have only to analyze the pathogenesis of the convulsions that follow removal of the pituitary to realize that the rôle of its test organ is also to prevent general intoxication in the higher animals, including man. This procedure, as observed by Marinesco,²⁴ Vassale and Sacchi,²⁵ Masay,²⁶ and others, produces, as Schäfer²⁷ expresses it, "muscular twitchings and tremors developing later into spasms." This exemplifies the familiar convulsions caused in children by autointoxication; those ascribed

²³ Overton: *Ibid.*, cv, p. 176, 1904.

²⁴ Marinesco: C. r. de la Soc. de biol., p. 509, 1892.

²⁵ Vassale and Sacchi: Arch. ital. di biol., xxii, p. 133, 1895.

²⁶ Masay: *Loc. cit.*

²⁷ Schäfer: "Textbook of Physiology," I, p. 946, 1898.

to tetanotoxin; those of puerperal eclampsia which Williamson,²⁸ Grandin,²⁹ and others ascribe to poisonous substance circulating in the blood; those provoked in animals by Herter,³⁰ Krainsky,³¹ and in man by Ceni³² with hypertoxic serum derived from epileptics, a fitting corollary for Pierce Clark's³³ conclusion, based on a study of 150,000 epileptic seizures, that "we must see the pathogenesis in an initial toxin or autointoxication." I have urged in this connection, and others besides myself have found, that in appropriate cases of epilepsy, those in which the thyroid is inadequately active and in which gliosis has not been given time to develop, thyroid extract proves effective in arresting the paroxysms. Need I refer to its corresponding action in the convulsions—of both tetanic and epileptic type—that follow extirpation of the thyroid and parathyroids? Here there is directly introduced into the blood the agent which sensitizes the toxic wastes and renders them vulnerable to the destructive action of the other defensive substances.

THE MODE OF ACTION OF THE IMMUNIZING MECHANISM AND THE GENESIS OF FEVER.—In view of the foregoing facts, physiological, clinical, histological, and zoölogical, the introduction of a toxic into the blood should, by exciting the test organ, awaken the defensive resources of the body to action through the intermediary of the thyroid apparatus and adrenals. Crucial experiments are available to show that such is the case, *i.e.*, that the test organ when excited by a poison stimulates the adrenals and the thyroid apparatus and thus induces destruction of that poison, and, moreover, that when the test organ cannot transmit its impulses to the adrenals and thyroid the autoprotective process does not manifest itself. These experiments were those of Sawadowski³⁴ and of other investigators referred to below. They indicate, when explained in the light of my views, that

Fever is the physiological expression of the defensive mechanism when a toxic capable of exciting the test organ is present in the blood.

²⁸ Williamson: *Obstetrics*, p. 703, 1903.

²⁹ Grandin: Grandin and Jarman's "Practical Obstetrics," p. 94, 3d ed., 1906.

³⁰ Herter: *Jour. of Nerv. and Ment. Dis.*, February, 1899.

³¹ Krainsky: *Wiener klin. Woch.*, February 24, 1898.

³² Ceni: *Riv. Sper. di Fren.*, xxxi, No. II, 1905.

³³ Clark: *Medical News*, July 18, 1903.

³⁴ Sawadowski: *Centralbl. f. d. med. Wissen.*, 26th year, No. 9, p. 181, 1888.

I have urged that the pituitary contained the heat center, and that it produced a rise of temperature through the intermediary of the adrenals and thyroid. The test organ is evidently closely connected with the heat center, for the protective process it awakens when certain poisons occur in the body is a rise of temperature. Now, Sawadowski noted, after injecting putrid substances into the blood, and in accordance with familiar experience, that it caused fever, even *after the cerebrum had been removed* from the midbrain. He found, moreover, that antipyrin controlled this fever. But his experiments revealed an important fact, viz., that section through the optic thalami or the posterior edges of the corpora striata (which, from my viewpoint, also severed the nerve paths from the test organ or heat center to the adrenals and thyroid) prevented these effects. "After these sections," he writes, "neither the putrid materials nor the antipyrin exerted any influence upon the temperature. The sinking of the temperature was not arrested by the putrid substances." The last statement refers to the fact that, notwithstanding the presence of putrid substances which had caused fever, the temperature steadily went down—after the operation—from 38.1° C. in the colon to 31.4° C. This recalls the steady decline that occurs after removal of the pituitary. Ott and Scott³⁵ also found that the marked rise of temperature that follows the intravenous injection of betatetrahydronaphthylamin in normal rabbits did not occur after they had transected the base of the brain behind the tuber cinereum.

The heat, or thermogenic, center thus influenced cannot be located in the cerebrum, for we have seen that removal of this organ does not affect the temperature. Nor can it be located in the optic thalamus or the corpus striatum, for Ott and Harris³⁶ provoked the typical rise of temperature by puncturing with a needle, through the mouth, "only the lower surface of the tuber." Its true location is shown by the fact that Ott found a thermogenic center in the anterior portion of the floor of the third ventricle, *i.e.*, immediately above the pituitary. Moreover, it is precisely traversed by the nerves which Andriezen, Gentès,

³⁵ Ott and Scott: Jour. of Exper. Med., November, 1907.

³⁶ Ott and Harris: Therap. Gaz., June 15, 1903.

Joris, and others traced from this organ, and which Andriezen followed to the region of the pons.

Under these conditions, however, transection of the pons should also have prevented the thermogenic action of putrid materials in Sawadowski's experiments. Such proved to be the case. Of this experiment, carried out with the aid of Pawlow, Sawadowski writes: "Following out Ischetschichin's method, a diagonal section was made through the pons Varolii. When the section was complete, free from hæmorrhage or of any condition which might excite the surface of the cut tissues, a gradual diminution of the temperature occurred in the rectum and between the toes. In one experiment, for example, in which the preoperative temperature was 38° C. in the rectum, and 34.5° C. on the skin, nine hours after the operation the first had fallen to 27° and the second to 25° C." This applies as well to the spinal cord; "when the section was made quite high up," he says, "no rise of temperature could be obtained with putrid materials, nor did the antipyrin lower it."

In the portion of the cervical region, however, he found that transection of the spinal cord did not completely prevent the influence of either the putrid materials or the antipyrin. But we have in this paradoxical phenomenon only confirmatory testimony to the presence of a nervous connection between the pituitary and the thyroid apparatus, for in these "low sections," as he terms them, he severed the cord below the origin of the nerves to the thyroid, thus leaving untouched the nerves which connected it with the pituitary and its test organ, though severing the path to the adrenals. What effects were obtained were due to the thyroid apparatus, which remained under the influence of the test organ, and therefore of the thermogenic poison and antipyretic.

These experiments speak for themselves—especially in view of the fact that Sawadowski mentions among the concomitant effects of his sections "disorders of respiration and circulation," and also blueness of the blood—obvious evidences of defective oxygenation. Added to the foregoing evidence, they seem to me to warrant the following general deductions:—

1. *Man, in keeping with many animals lower in the phylogenetic scale, is supplied with an autoprotective mechanism.*

2. *This mechanism includes: 1, the immunizing center, an organ of special sense annexed to the heat center, both centers being located in the pituitary body; 2, the thyroparathyroid glands; 3, the adrenals, and, 4, special nerves which connect the immunizing center (or overactive heat center) with these two sets of organs.*

3. *The immunizing center, which governs the autoprotective mechanism, is the developed "osphradium" or "test organ" described by zoölogists in mollusks and certain ancestral vertebrates.*

4. *While the osphradium of primitive animals tests their respiratory fluid, sea water, its prototype, the immunizing center of higher animals, including man, tests the blood, also a respiratory fluid and a qualitative homologue of sea water.*

5. *When the functional activity of the immunizing center is increased through the presence in the blood of some toxic, i.e., wastes, toxins or endotoxins, mineral and vegetable poisons, certain venoms, drugs, etc., capable of exciting this center, it stimulates correspondingly the heat center and thus awakens the immunizing process.*

6. *Fever indicates that the autoprotective mechanism is active. The rise of temperature is due to the increased production of thyroparathyroid and adrenal secretions, and the resultant increment of metabolic activity. The immunizing process is a consequence of this hypermetabolism, all the immunizing agents, plasmatic and cellular, being produced in greater quantities.*

But Lazarus Barlow states we have seen—and he is amply sustained, I may add, by the teachings of clinical experience—that "in pneumonia, erysipelas, cerebrospinal meningitis, typhoid fever, the prognosis is better if the patient's temperature is moderately high than if it is definitely low." This is met by the interpretation of the febrile process I submit in the next conclusion:—

7. *Absence of fever in a toxæmia of any kind is due to inability of the immunizing center to react under the influence of the toxic, owing to deficient sensitiveness (inherited or acquired) of this center, or to the fact that the toxic is itself a paralyzant or anæsthetic of its sensory elements.*

On the other hand, every practitioner is aware of the dangers of hyperpyrexia. This also finds its normal explanation in the terminal conclusion that:—

*8. Excess of fever (above 105° F.) is due to excessive excitation of the immunizing center and a corresponding overproduction of defensive bodies. This condition exposes the red corpuscles and the endothelial cells to proteolytic destruction (hæmolysis and autolysis) along with the pathogenic substances or bacteria.*³⁷

CONCLUDING REMARKS.—Such are the facts which have led me to believe that the human organism is supplied with an auto-protective mechanism. Its functions, I may add, harmonize with the views of the modern biochemist who has found that increased metabolism is a characteristic of the febrile process; they also coincide with the observations of the bacteriologist that, while most pathogenic bacteria thrive at the normal temperature of the body, they promptly die when it is raised several degrees. They account for the teaching of clinical experience that a higher mortality occurs in apyretic cases than among those in which the febrile process had been active. They explain the harmful influence of hyperpyrexia, since excessive immunizing activity means proteolytic destructions of the blood-cells (hæmolysis) and even of tissue-cells (autolysis) besides the pathogenic agents themselves.

In the practical field, personal experience sustained by that of many colleagues who have carefully studied my doctrines has shown clearly that these embody the lever through which we can overcome infections. We need only analyze the beneficial action of vaccine therapy, of antitoxin, of drugs such as mercury, the iodides, and other so-called “alteratives,” to recognize that their tendency, in therapeutic (non-toxic) doses, *is to raise the temperature*—PROOF THAT THE IMMUNIZING PROCESS IS ACTIVE.

Yet, as is well known, the autoprotective resources of the body do not depend only upon the germicidal and autotoxic constituents of the blood-plasma. Indeed, they could not be

³⁷ The placing of animals in the heated chamber to determine the influence of high temperatures on the corpuscles is a useless and misleading experiment, since the proteolytic ferment, the active agent in the process, is not increased.—S.

carried out without the potent co-operation of the phagocytes, the importance of which in immunity has been revealed to us through the genius of Metchnikoff.

To obtain an idea of the relations of the internal secretions with these defensive cells, we should have at least an idea of their relations with the ductless glands, the manner in which the vital process is sustained in them, and the rôle each type of leucocyte fulfills in this connection. I know of no work in which these features are studied and must, therefore, build up the whole framework of the process, and thus try, at least, to ascertain the nature of the connection between the immunizing process as I have described it in the foregoing pages and the functions of the phagocytes.

THE LEUCOCYTE IN ITS RELATIONS TO NUTRITION, ORGANIC FUNCTIONS, AND IMMUNITY.

Before inquiring into the physiological functions of each of the various varieties of white corpuscles, or leucocytes, it was deemed advisable to study the cell as a unit, and particularly the functional attributes of its main component structures: (1) the nuclear and cellular reticulum or mitoma; (2) the granules.

THE MITOMA.—Alluding to basophile leucocytes, Howell^{7a} states that the nucleus “is divided into lobes that are either entirely separated or are connected by fine protoplasmic threads.” This is well illustrated in the annexed plate from a valuable study of the subject by G. L. Gulland,³⁸ by Fig. 1, a hyaline leucocyte from a newt’s blood. These cells are undeveloped and their protoplasm does not as yet show “threads.” But their nucleus is clearly supplied with them even at this early stage—a feature which suggests that the nucleus is an autonomous structure. This is further sustained by the presence, in the perinuclear portion of the cell, of a small body, the astrosphere, shown in Fig. 7, another undeveloped, or “hyaline,” cell. This astrosphere is likewise present in fully developed leucocytes, as may be seen in Figs. 10, 12, and 16. Each cell

^{7a} Howell: *Loc. cit.*

³⁸ G. L. Gulland: *Journal of Physiology*, vol. xix, 1896.

may, therefore, be said to contain two functional centers, each supplied with its net-work of fibers or threads.

Heidenhain is stated by Gulland to have found that "the granules are arranged radially to the astrosphere, with the smallest granules next the sphere, the largest at the periphery." This is exemplified with especial clearness in Figs. 10 and 16, and if the threads, or fibers, are traced from the center of the astrosphere, the gradual increase in size of granules as the periphery of the cell is approached is clearly indicated. Heidenhain also concluded, a feature fully confirmed by Gulland, that "there are never any granules within the astrosphere itself." It thus becomes evident that, while the nucleus is an autonomous structure, the same may be said of the astrosphere. In other words, a leucocyte seems to be supplied with two individual, though doubtless correlated, functional systems: (1) the nucleus *per se*, which contains a net-work of fibrils and granules; (2) the astrosphere, which represents the center of the cellular net-work of granule-laden fibrils.

As may be seen, in the numerous cells represented in Gulland's plate, which cells have been drawn by him with the utmost care and fidelity to microscopic appearances, the fibers in the nucleus divide the latter into several irregular areas, while the radiating net-work of which the astrosphere is the center forms relatively regular spaces. The fibers in both structures run to their external boundaries, however, precisely as if they were attached to the external limiting membranes of each. And yet the nucleus alone seems to be supplied with such a membrane, while the surface of the cell is not. A prominent feature of these cells is the fact that their protoplasmic exterior is absolutely bare.

After a study of the characteristics of the granules, Gulland writes: "The granules of leucocytes are therefore *not* products of the metabolic activity of the cell imbedded in a structureless protoplasm, as was hitherto supposed, but represent an altered condition of the microsomes [the granules]. They always form part of the cytomitoma [the net-work of fibers] and are therefore *plasmatic*, and not *paraplastic*. They are probably concerned with amœboid movement, and they and the rest of the mitoma are more visible the more active the cell."

Fig. 8

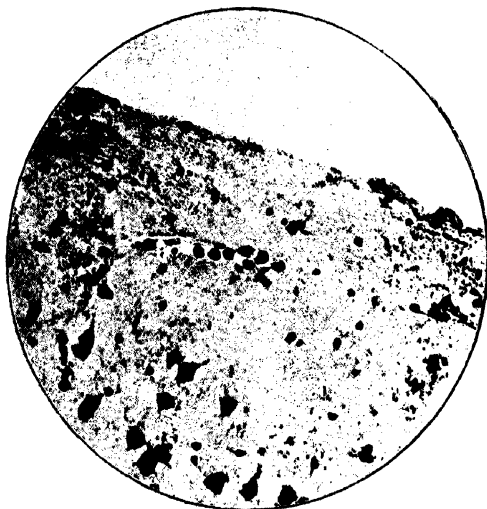
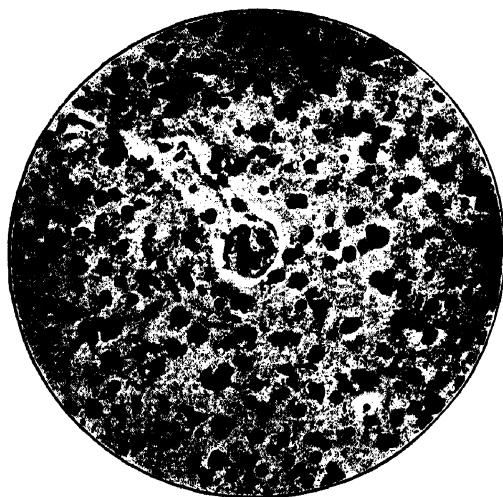


Fig. 9



LEUCOCYTES IN THE PERIVASCULAR SPACES AND
IN VESSELS, AS A RESULT OF ACUTE ALCO-
HOLIC POISONING. [*Berkley.*]

[*Johns Hopkins Hospital Reports.*]

Granules, as the plate distinctly shows, are plentiful within the nucleus, and in the cellular substance likewise; in fact, in the latter they are crowded around the centrosphere, the deepest portion of the cell.

If the granules are plasmatic, *i.e.*, formed by substances derived from the plasma, how does the latter reach the minute areas in which the granules are formed? Channels seem to me absolutely necessary for the passage of the blood-plasma, its alkaline phosphates, and other plasmatic salts from which the granules are formed.

The prevailing view that the threads (mitoma) are concerned with the amoeboid movements of leucocytes, as also inferred by Gulland, is by no means, it seems to me, incompatible with the possibility of their being plasma-channels, or efferent canaliculi. Indeed, their elasticity does not eliminate the possibility of their being tubular, while their extension and retraction may, as in the sweat-glands, afford the mechanical elements of an expulsive process. "It is certainly interesting to note that, the more active the cells of this series become," writes Gulland, referring to the acidophile (phagocytic) leucocytes, "the more visible become their mitoma and the microsomes which form part of it. The lymphocytes in which no mitoma can be seen are practically non-amoeboid. The hyaline cells in which it is not very evident move but sluggishly. The oxyphile cells, with a well-marked mitoma and microsomes, move more rapidly, and the eosinophile cells, whose mitoma and microsomes are the most visible of all, move most rapidly." Again, he says: "It is certain that the length of thread lying between the microsomes varies immensely in different parts of the cell, and the short threads are usually the more deeply stained; so that it looks as though they were *contracted* and therefore *thickened*. On the other hand, the microsomes at the periphery are, generally speaking, the largest, and there can be no doubt that it is the circumference of the cell which moves most and moves farthest." As regards the basophile leucocytes, he states that, "as far as one can judge from fixed specimens, the larger basophile cells seem to have more power of movement than the smaller ones"—a feature easily accounted for, since they are not bactericidal, as are the acidophile leucocytes.

It seems probable, however, that in both acidophile and basophile cells the fibers take part in the mechanism through which they travel in the plasma, while contraction, thickening, etc., *i.e.*, the elements of a suction or expulsion process, are present to suggest the identity of the mechanism to which they owe their powers of locomotion.

Basophile leucocytes are not phagocytic; they do not, therefore, ingest foreign substances as do the latter, *i.e.*, by inglobing them. They must, therefore, be provided with a different mechanism for this purpose. If, in accord with my view, the mitoma represents a system of centrifugal canaliculi, it cannot serve for this purpose. Indeed, the external agencies penetrate the cell to the nucleus itself. Thus, W. R. Stokes and A. Wegefarrth,³⁹ alluding to the researches of Bail,⁴⁰ say: "After injecting virulent staphylococci into the pleural cavity of rabbits he found that the leucocytes underwent a characteristic change. They formed round, empty bodies, containing several vacuoles in the *nucleus*."

How did the virulent staphylococci reach the nucleus's vacuoles? Metchnikoff's plate (opposite page 692 in this volume) will assist us in elucidating this question. It not only forcibly illustrates what this distinguished zoölogist sought to show, but likewise, it seems to me, a mechanism of ingestion, differing somewhat from the recognized "ingulfing" or "inglobing" process through which phagocytes take up germs, small particles, etc. An example of this mode of appropriating various plasmatic or foreign substances is illustrated in Fig. 5, which shows bacteria penetrating, from various directions, *into* the cell-wall, while Fig. 16 shows the bacteria *within* the perinuclear vacuole. As all the cells in Metchnikoff's plate are phagocyte, the mechanism of ingestion to which I refer is not only that of basophiles, but is obviously a feature of all leucocytes.

The fact must be emphasized that I say "perinuclear" vacuole, and not "nuclear" vacuole, for, if this and the other germ-laden cells just referred to are carefully examined, it will become evident that the bacteria lie in a pocket contiguous to,

³⁹ W. R. Stokes and A. Wegefarrth: Bulletin of Johns Hopkins Hospital, Dec., 1897.

⁴⁰ Bail: Berliner klin. Wochenschrift, Oct. 11, 1897.

but not forming part of, the nucleus itself. I would not say, therefore, with Bail, "vacuoles *in* the nucleus," but vacuoles *around* the nucleus. Indeed, Gulland refers to Heidenhain as considering that "the nucleus lies free in the interfilar spaces, and is not organically connected with the cell-substance." This is quite in accord with my view, and it seems to me that it represents the cavity into which bodies ingested by leucocytes normally arrive, though smaller vacuoles are likewise present in the cytoplasm.

The actual presence of this perinuclear vacuole from which canaliculi would start appears to me indicated in several of the figures in the annexed Gulland's plate. Fig. 8, for instance, stained with iron-hæmatoxylin, shows that the nucleus is surrounded by an irregular limiting material of some kind; but if we compare the outline of this limiting substance with that of all the succeeding cells, an interesting feature asserts itself, viz.: its thickness is extremely variable. Although 12 may be said to be moderately regular, the others, in the following sequence: 11, 10, 13, 8, 9, and 14, are increasingly irregular. If, now, this irregularity itself is scrutinized, a significant fact is revealed: i.e., the bulges, or projections, in the limiting structure are all at the expense of the nucleus. In Fig. 9, for instance, just above a clover-like figure near the center of the cell (probably the astrosphere), the marked bulging shows every evidence of having been formed by a substance which had compressed the nuclear substance inwardly. The stages of this compression are exemplified in Metchnikoff's plate, by Figs. 16 and 15, successively. In the former a single mass of liquid and germs is seen to have indented the center of the nucleus on one side, while in the second figure three cavities are shown which have distorted it. (The nucleus is indicated by an *n*.) In *both*, however, the compression has exceeded the normal boundaries of the limiting structure, and centrifugal bulging has occurred at the expense of the perinuclear protoplasm or cytoplasm. So marked has this become in Fig. 14 that the nucleus is not discernible.

The identity of the mitoma as a system of canaliculi suggests itself in another way. I have shown that the axicylinders of nerves, neuroglia fibrils, etc., contained blood-

plasma. Such being the case, if the fibers or "threads" in leucocytes are likewise plasma channels, they must stain, as do the former, when treated to various dyes. We have seen (pages 541 to 543) that methylene-blue dissolved in salt solution and injected into the vessels of a living animal colored the axis-cylinders blue, according to Ehrlich, and that this investigator defined the conditions of nerve-structure essential to the methylene-blue reaction as "oxygen saturation and alkalinity"—the very attributes of blood-plasma. Referring to the various stains used by him, Gulland says: "In examining the basophile cells I used almost entirely various methylene-blue solutions," and, later on: "The basophile cells of the dog's intestinal villi, when fixed with absolute alcohol and stained with alcoholic methylene-blue, give exactly the same results, as to mitoma and granules, as other basophiles." Evidently, as regards the methylene-blue stain, nerve-fibrils and mitoma (my canaliculi) are similar. Again, besides the plate reproduced here, Gulland presents two colored plates, in which the characteristic affinity of each cell for stains appears; the six basophile leucocytes stained with methylene-blue (normal) distinctly show that structures which stain most deeply are the chromatic, *i.e.*, the nuclear mitoma; then, more faintly, the cellular mitoma. It seems clear that, as regards methylene-blue stain at least, the conditions are similar to those of nerves as far as the mitoma—or canaliculi—are concerned.

The same correspondence exists between nerve-fibrils and the mitoma when hæmatoxylin is used. We have seen (page 536) that, according to McCarthy, the rods that project radially from the axis-cylinder "stain with carmine and hæmatoxylin, which do not stain the myelin." The fact that the axis-cylinder takes hæmatoxylin hardly needs to be emphasized, its use in histological laboratories when nervous structures are studied being second only to picrocarmine for general staining. A beautiful example of hæmatoxylin-stained human cerebrospinal and sciatic nerves is to be found in Clarkson's "Histology," page 204, for instance. All the eosinophile leucocytes shown in the annexed plate, in which the nuclear and the perinuclear granules and mitoma are so clearly defined, were stained with Heidenhain's iron-hæmatoxylin, which only differs from

the usual solution in that it colors the cellular elements that take it a dark gray or black. This also shows that it is not only with the mitoma of basophile leucocytes that the staining characteristics of nerve-fibrils—*i.e.*, plasma-containing channels—coincide, but also with that of eosinophile cells. Even Apáthy's fibrils are recalled by the effects of corresponding stains, for Senn writes,⁴¹ referring to the minute anatomy of the leucocyte: "The reticulated structure is well shown by staining with chloride of gold, which stains the protoplasmic *strings*, but not the interstitial substance." It seems quite evident, therefore, that *the mitoma*, *i.e.*, *the intracellular and intranuclear networks of fibers in mature leucocytes, are canaliculi for blood-plasma.*

FUNCTIONAL MECHANISM OF THE LEUCOCYTE.—I have expressed the view that the nuclear canaliculi open into a vacuole which surrounds the nucleus (see Fig. 14 in Gulland's plate) and that the outer wall of this vacuole acts as terminal for some of the canaliculi of the cell-substance. Although, as suggested by Fig. 11, the canalicular orifices that open into the vacuole from both directions may correspond (the nuclear orifices being in that case opposite the cellular openings), such is by no means always the case. Indeed, in Fig. 16, for example, but two or three of the external canaliculi seem to be connected with the vacuole, while this cavity serves as terminal for all the *intranuclear* channels—if such they are.

Is the connection between this vacuole and the exterior of the cell direct or indirect: *i.e.*, through separate channels leading directly to the exterior or to those connected with the astrosphere's system? That the communication is independent of the latter is emphasized by the presence of granules in the path of all canaliculi, as shown in Gulland's plate. A continuous function depending upon an inflow of plasma would obviously be in constant danger of arrest were the granular channels centripetal pathways. Again, in all leucocytes, acidophiles as well as basophiles, the nucleus stains in the same manner, the granules alone, as we have seen, showing variations in this particular. The same may be said of the reticulum, for we have seen, by the staining reactions, that the compounds com-

⁴¹ Senn: "Principles of Surgery," 3d ed., 1901.

posing the granules are bathed in oxidizing substance, *i.e.*, adrenoxidase. This uniformity of nuclear and cellular fluids in the canaliculi suggests the presence of a very common mechanism—one, indeed, which must serve to *eliminate* its contents, judging from the fact already mentioned, that the intracellular granules increase in size outwardly, the largest granules being at or near the surface. A common centrifugal canalicular system again suggests the presence of a system common to all leucocytes, whether phagocytic or not, for the introduction (not necessarily of particles or other discernible agencies) of more or less liquid or viscid bodies required by the cell for its own nutrition, or connected with its own physiological functions: *i.e.*, the elaboration of granules. The canaliculi serving only for the centrifugal elimination of the latter, the centripetal paths must penetrate to the vacuoles *between* the canaliculi, or “threads,” as already explained, and as shown in Metchnikoff’s plate, Fig. 5. We are evidently not dealing here with mere inclusion or pseudopodial flowing around the germs, for the latter may be seen to penetrate the cell between the granules, and, judging from Figs. 13, 14, 15, and 16, directly into the perinuclear vacuole itself.

Is the cell supplied with *centripetal* canaliculi *in addition* to the centrifugal system which I believe to be represented by the reticulum? The fact that micro-organisms can penetrate directly *into* the vacuole between the external layer of granules is not alone to suggest that such is the case, but the manner in which the leucocyte takes up stains likewise does so. As can readily be seen, the absorption of the dye by the cell occurs without involving any alteration of its shape which can at all be associated with the process. That the absorption cannot occur through the visible canaliculi: *i.e.*, those that take stain because they constantly contain fluid, is rendered very probable by the presence of the granules, which must entirely close their external orifices. It must occur, therefore, through paths presenting some analogy to the pores of certain sponges, which allow the surrounding water to pass into the interior of the sponge, so long as it does not carry any harmful products along with it (Metchnikoff). And yet the fact that such a system of channels does not exist is shown by the promiscuous

directions taken by bacteria in penetrating into the cell. Indeed, their bodies are not directed axially toward the perinuclear vacuole; they seem, once within the external layer of granules, to point in almost any direction. We are brought back, therefore, to the soft, yielding, protoplasmic cell-substance of the amœba, which will allow liquids to transude easily through it, and the more dense materials to cleave their path into it and down to the vacuole, without leaving a wound behind them. "On introducing pigeon leucocytes filled with anthrax bacilli (to which the pigeon is very refractory) into bouillon," says Metchnikoff, "bacilli grow, *pierce* the protoplasm of the cells, and form well-developed filaments, showing definitely that the bacilli were inglobed in a living condition." We might say "ingest," however, for the perinuclear vacuole asserts its identity as a digestive organ—the familiar digestive vacuole—in several ways: *i.e.*, as a cavity in which all the materials that supply the cell with functional energy—*i.e.*, with life—are drawn.

Metchnikoff,⁴² referring to the intracellular digestion to which amœbæ submit the materials they engulf, writes as follows: "A closer observation of the group of protozoa compels us to the conviction that this digestive function must play an important rôle in the mutual relations of these lowly organisms. Many rhizopoda and infusoria live in media swarming with other unicellular organisms, including bacteria. The latter, which multiply very rapidly, serve as food to many of the protozoa. Thus, various amœbæ devour bacilli, which undergo certain definite changes in the interior of the protoplasm. Without altering their shape, the bacilli acquire the power of taking up solutions of vesuvin, which does not stain these microbes when living in their natural conditions. Since precisely similar changes are also observed in the interior of vorticellæ and infusoria, which live on bacteria, it is evident that they are due to a digestive influence exerted by the contents of the protozoa." This conclusion is in harmony with the observation of B. Hofer⁴³ on digestion in amœbæ. This investigator has shown that "the more the food is altered in the in-

⁴² Metchnikoff: "Lectures on the Comparative Pathology of Inflammation," translated by F. A. and E. H. Starling, pp. 18 *et seq.*, 1891.

⁴³ B. Hofer: *Jenaische Zeitschrift*, vol. xxiv, 1889.

terior of these rhizopods, the more easily does it stain with aniline dyes." When we consider that aniline dyes include methylene-blue, we have evidence, in view of Ehrlich's observation, that the "conditions essential to the methylene-blue reaction" are "oxygen saturation and alkalinity," that the prototype of amoeba, the leucocyte, must owe its nuclear functional activity to the plasma as exogenous reagent.

Metchnikoff further says: "We may often see flagellated monads taking up filaments of leptothrix several times as long as themselves, and finally inclose them in their digestive vacuoles." The process of ingestion is beautifully shown in the plate opposite page 692, in Figs. 19 and 20, the organisms here being spirilla of Asiatic cholera. "It is sometimes possible to follow all the changes undergone by the bacteria within an infusorium," continues the same investigator, "as in the case of the digestion by stentor of the sulphobacterium thiocystis, observed by le Dantec."⁴⁴ . . . "It is evident that the digestive function of the protoplasm of the protozoa must hinder the invasion of these animals by the lower organisms, and it is only in certain special cases that the latter can live as parasites within the rhizopoda and infusoria."

The true identity of the perinuclear vacuole seems further emphasized by the following lines, also quoted from Metchnikoff's text, that is to say, as interpreted by his translators: "The sponges are of such undifferentiated organization that they were long considered to be colonies of protozoa, consisting, like the protospongia, of separate flagellated and amoeboid individuals. Later on, it was, however, ascertained that they bore a certain relationship to the polypi and their allies (coelenterata)." . . . "There are a few species, such as the siphonochalina coriacea, whose mesodermic cells alone inclose all foreign bodies, so that the cylindrical cells of the endoderm merely serve to keep up the continuous passage of the fluid through the sponge. The *phagocytes* of both layers have the power of rejecting insoluble matters, which collect in the larger efferent canals." . . . "We are, however, chiefly concerned here with the fact that the mesodermic *phagocytes*

⁴⁴ Le Dantec: "Recherches sur la digestion intracellulaire," Lille, 1891.

are able to *digest* the substances as well as to inglobe them, and to *reject* the insoluble residue."

The nature of the digestive process has, however, remained obscure. "The bacilli which have been inglobed by leucocytes," continues Metchnikoff, "are much more rapidly digested in the case of mammals that are either naturally refractory, as the dog and fowl, or have been rendered artificially immune against anthrax by vaccination, as the rabbit. This fact is shown by the researches of Hess, as well as my own. It is easy to follow the digestion of many other microbes within the leucocytes. Vacuoles are often seen to form around the bacteria that have been swallowed, just as we have noticed in the digestion of nutrient material by the protoplasm of the protozoa and the myxomycetes. I have been able to observe the changes undergone by the spirilla of recurrent fever in the leucocytes of monkeys, as well as those undergone by the vibrio septicæmiæ in the leucocytes of immunized guinea-pigs, and those by erysipelas streptococci in the leucocytes of man, etc. We are at present ignorant of the precise manner in which this digestive and destructive action is accomplished, and do not even know whether the substance which kills the microbes is a ferment or not."

Before submitting this question to analysis the manner in which the products of digestion, both the nutritional elements and the excrementitious products, are disposed of must be ascertained.

In the sponge the materials rejected by the phagocytes "and which collect in the larger efferent canals," says Metchnikoff, are eliminated "through large apertures of crater-like shape, the walls of which, according to some authors, are furnished with muscular fibers." What have we in the leucocytes to fulfill this function: *i.e.*, to represent what in the higher forms constitutes the intestinal canal? This appears to me particularly well shown in several of the figures in Gulland's illustration. In Fig. 10, for instance, a few "fibers"—our canaliculi—may be seen to project from the inner aspect of the line which to me represents the practically empty side of the vacuole. The same arrangement is clearly to be seen in Figs. 11, 12, 13, and 16.

If all the foregoing features are considered collectively, they suggest that:—

1. *Leucocytes can ingest solid, semisolid, and liquid bodies through their cell-substance in two ways: (1) by projecting pseudopodia which infold or inglobe them; (2) by absorbing them without projecting pseudopodia.*

2. *Solids and semisolids are mainly ingested by infolding, and semisolids and liquids by absorption; but all substances, with what plasma accompanies them, are collected in a vacuole that surrounds the nucleus and in which the latter lies free; and, at times, in the smaller vacuoles in the cytoplasm.*

3. *What physiologically useful bodies are formed in the cell are mainly elaborated in the nuclear canaliculi and the perinuclear vacuole, and are collected in the form of granules in the canaliculi.*

4. *All the functions of the cell are probably governed by the astrosphere.*

THE GRANULES AS SECRETORY PRODUCTS.—Gulland refers to granules or microsomes in the following words: "Ehrlich regarded the seven varieties of granules which he described as being all formed by the cells, and as being either reserve material or products for excretion. Hankin [1892-93] took the view that the acidophile granules were secretory products, containing 'alexins,' and destined to be secreted into the blood or lymph. Kanthack, Hardy, and Keng have taken much the same view of these special granules. Sherrington has thrown doubt upon it, and Metchnikoff disputes it and regards the eosinophile granules as reserve material." As viewed from my standpoint, the granules simultaneously represent reserve material *and* products of excretion. These processes are not the only ones, however, with which leucocytes are concerned.

Bail, to whose investigations I have already referred, is also stated by Stokes and Wegefarth⁴⁵ to have observed that, after the vacuole "in the nucleus" had formed, "the granules generally disappeared." Furthermore, he noted that upon destroying the staphylococci by adding ether, and diluting the centrifugalized sediment, the granules showed a dancing motion, and were seen to *leave the periphery of the cell and enter*

⁴⁵ Stokes and Wegefarth: *Loc. cit.*

the surrounding medium. Evidently at least *some* of the granules must have been dropped or ejected by the leucocytes, and their canaliculi thus freed of the impediment their presence constituted.

This is sustained by a closer examination of the question, —the purpose of Stokes and Wegefarth's paper, who used in their researches blood taken from about five hundred persons. The granules, when observed by them with the aid of artificial light, "resembled those of the eosinophilic or neutrophilic leucocyte." Kept at the temperature of the room, the latter showed no activity, but exposure for an hour to a temperature of 35° C. caused them to become active. The following lines are quoted from their article: "At times the granular leucocytes become actively amœboid, and the granules *within* the neutrophile exhibit a characteristic activity which might be compared to the swarming of bees around a hive. The number of fine granules free in the plasma is perceptibly increased. The eosinophilic granulations also show a less vigorous tremulous motion, and both varieties follow the changes in the direction of the pseudopodia, the protoplasm being thrown out first, and the granules following. The characteristic dancing motion of the granules in the neutrophilic leucocyte can be brought out very plainly by simply mixing the drop of blood with an equal amount of distilled water containing 1 per cent. of alcohol. The granules become very active and present a characteristic picture." . . .

"Can these granules be actually seen to leave the leucocyte? It is certainly not easy to be sure, even after continuous observation for an hour or more, that one has actually seen one of these granules leave an amœboid leucocyte. We think, however, that we have observed this phenomenon upon several occasions, both in fresh specimens of blood exposed to 35° C. and in blood to which 1 per cent. of alcohol has been added." Farther on in their text they say: "Many fine granules can be seen in the clear plasma and around the neutrophile, and it would seem that occasionally a granule leaves the active leucocyte and becomes free in the surrounding fluid."

Bail's observation, however, that the granules actually leave the periphery of the cell has been sustained by other

observers. Gulland refers to this feature of the problem in the following words: "It has often been remarked that the large cells show a great tendency to leave their granules behind them; thus, one might come on a group of granules while the nearest cell was far away. Ballowitz was, I think, the first to declare that all or most of these groups of granules were attached to the cell by fine protoplasmic bridges. It is not always easy to show this." Gulland then says, referring to a figure in one of his plates (not shown in that reproduced herein), in which the granules are evidently disunited from the cell: "In the cell shown in Fig. 31, which was so isolated that there could be no doubt that all the granules represented belonged to it, no trace could be made out of threads extending from granule to granule. They are probably stretched too much to allow them to be visible."

The absolute separation of the granules from the cell witnessed by Bail finds its complementary confirmation in the observation of E. B. Sangree,⁴⁶ who, after patient watching,—sometimes several hours at a time,—states that he saw "three granules escape from an eosinophile cell, and wander away until lost under rouleaux of red corpuscles, after having reached a distance of some six diameters from the parent-cell." . . . "While inside the cell," says this pathologist, "these granules had participated in the constant, though rather sedate, movements of the granule mass,—but owing, doubtless, to the difference in specific gravity of the containing medium,—instantly upon emerging from the parent-cell they underwent the wildest possible gyrations. The first to come out were two attached pole to pole, and these rolled frantically over each other, pushed this way and pulled that, all the time oscillating widely and rapidly, yet constantly and definitely traveling farther and farther from the cell, until finally lost to view. The single granule behaved in an exactly similar way. I noticed, too, that before becoming lost to view the motion of these granules had become considerably less marked and approximated more that ordinarily seen in these bodies." If these facts are considered as a normal sequence to the evidence adduced that the cellular

⁴⁶ E. B. Sangree: Philadelphia Medical Journal, March 12, 1898.

net-work of fibers represents the secretory system of the leucocyte, it seems permissible to conclude that:—

The granules in leucocytes are the products of an intracellular metabolic process and represent a true secretion.

THE PHYSIOLOGICAL CHEMISTRY OF LEUCOCYTES.—A feature which clearly points to the autonomy of the nucleus and of the net-work of canaliculi in all leucocytes is the uniformity with which they all stain with similar dyes. The nuclear canaliculi and granules and the canaliculi of the cell-substance all take the aniline dyes, methylene-blue and methyl-green, for example: evidence that in *all* leucocytes the structures mentioned must find in the adrenoxidase a source of energy as do other organs.

Beginning with the nucleus, with what chemical body contained in this part of the cell could the adrenoxidase initiate and sustain a reaction? It is, of course, not the composition of the nuclear *granules* that this question involves, but that of what might be termed the nuclear ground-substance. Foster refers to this substance in the following words: "There is present, in somewhat considerable quantity, a substance of a peculiar nature, which, since it is confined to the nuclei of the corpuscles, and further seems to be present in all nuclei, has been called *nuclein*. This nuclein, which, though a complex nitrogenous body, is very different in composition and nature from proteids, is remarkable, on the one hand, for being a very stable, inert body, and, on the other, for containing a large quantity (according to some observers, *nearly 10 per cent.*) of *phosphorus*, which appears to enter more closely into the structure of the molecule than it does in the case of proteids." We evidently have, in the nuclein of the nuclear ground-substance, a body which, as does lecithin in the myelin of nerves, myosinogen in muscles, etc., enters into active combination with the oxidizing substance, *i.e.*, adrenoxidase, and the resulting reaction must necessarily yield functional energy, as elsewhere in the organism.

The character of the reaction which the simultaneous presence of nuclein and the oxidizing substance within the precincts of the nucleus sustain is clearly suggested by the kind of dyes taken by the canaliculi (both of the nucleus and of the

cell-substance) and the perinuclear vacuole. E. T. Williams,⁴⁷ in a study of the chemical properties of leucocytes, refers to this feature of the problem in the following words: "The nuclei of all three classes stain best with alkaline dyes, as methylene-blue, methyl-green, or dahlia. They are, therefore, acid." Farther on, he says: "We have seen that all nuclei are acid. They owe this property, without doubt, to the nuclein which they contain. Nuclein is acid. When boiled *with alkalis* it yields phosphoric acid. Phosphoric acid, it may be remarked, is the only mineral acid which does not coagulate albumin. It is the presence of this acid undoubtedly which makes nuclein acid. According to the experiments of Kossel, quoted by Vaughan and Novy,⁴⁸ nuclein, when boiled with acids, yields certain organic, albuminoid bases, as adenin, sarcin, xanthin, spermin, and others." . . . "We must conceive, therefore, of nuclein as some sort of a phospho-albumin whose composition has not been precisely determined." The source of the various chemical bodies involved in these processes is shown in the following lines of Professor Foster's: "The ash of the white corpuscles is characterized by containing a relatively large quantity of potassium and of phosphates, and by being relatively poor in chlorides and in sodium. But, in this respect, the corpuscle is merely an example of what seems to be a general rule (to which, however, there may be exceptions), that, while the elements of the tissues themselves are rich in potassium and phosphates, the blood-plasma on which they live abounds in chlorides and sodium salts."

The chemical process involved may easily be traced with the foregoing factors as main elements: The blood-plasma (if the views already submitted are sound) evidently reaches the nucleus through the intercanalicular substance of the cell-body; this is shown by the fact that this substance likewise—though to a less marked degree—stains with methylene-blue. Under ordinary circumstances, according to microscopical evidence, the perinuclear vacuole is practically collapsed: *i.e.*, its nuclear wall is more or less close to that of the cell-body. This is well shown in Gulland's plate, by Figs. 10 and 12. The nucleus

⁴⁷ E. T. Williams: Boston Medical and Surgical Journal, Sept. 5, 1901.

⁴⁸ Vaughan and Novy: "Ptomaines and Leucomaines," 1891.

thus bathes in blood-plasma, and its canaliculi become filled with the latter along with the vacuole. The nuclein of the nucleus under these circumstances itself bathes in the plasma, being thus exposed to the action of the latter's oxidizing substance or adrenoxidase.

Still, this suggests the presence of a stream of plasma flowing through the nucleus itself, with the canaliculi as emunctories. The contraction and retraction of the canaliculi—or reticulum—to which Gulland and others refer represent the only mechanical device in the cell by means of which the vacuole can be drained.

These minute vessels probably serve as continuous channels for the stream of plasma, which contains, besides the adrenoxidase, the alkaline salts necessary to the intracellular process. The plasma's adrenoxidase and the nuclein's phosphorus, thus brought into contact, liberate considerable heat, and the alkaline salts in the plasma then take part in the reaction to which Williams refers, and which involves, we have seen, the formation of phosphoric acid and other agencies to which I will presently allude.

We must not lose sight of the fact, however, that nuclein is derived from nucleo-proteids, and that during the oxidation process waste-products are formed: we have in the "adenin, sarcin, xanthin, spermin," etc., to which Williams refers, a series of catabolic products. This awakens an important pathological feature. We have seen that, when nucleo-proteids undergo cleavage in the organism, the process involved must be brought to a finish: *i.e.*, to the stage of phosphoric acid formation. The penalty, if completion does not attend the series of reactions, is the presence in the blood-stream of the above-mentioned purin bases, which are now considered, we have seen, as the source of the so-called "gouty diathesis." Slight insufficiency of the adrenal system, therefore, by reducing the adrenoxidase and thyriodase in the blood, must inhibit the intracellular reactions that I have just outlined, thus giving rise to this disorder. Or the injudicious use of rich foods, by surcharging the proportion of nucleo-proteids taken up by the cells, may lead to the same result though the normal proportion of adrenoxidase and thyriodase—the latter, we have seen, play-

ing an important rôle by sensitizing the phosphorus to oxidation—be present in the plasma.

Another phenomenon which appears to me elucidated by the presence of the adrenoxidase of the plasma is the manner in which worn-out leucocytes are destroyed. As frequently observed by histologists, each of the varieties may be seen at a given time to become "oxyphile," or oxygen-loving, and to undergo disintegration, a preparatory step to proteolysis here. Even the eosinophile leucocytes, which, according to Metchnikoff,⁴⁹ are unable "to inglobe foreign bodies, and therefore cannot act as phagocytes," are destroyed by proteolysis. The affinity of these cells for acid dyes might account for their oxidation, however, and suggest a limit; but such a limit does not exist, for basophile cells also yield to the same agency. Indeed, Gulland, referring to a figure in his colored plate which gives a vivid illustration of a cell undergoing disintegration, describes it as follows: "Degenerated basophile cell from the mesentery of newt. Methylene-blue." In other words, an eosinophile is always acidophile, while a basophile is only acidophile when it is dead or about to die. We have seen that methylene-blue stains oxygen-laden media; hence, the adrenoxidase is evidently an active factor (as amboceptor) in the destructive process.

It seems to me that we can conclude from the above data regarding the physiological chemistry of leucocytes, or white blood-corpuscles, that:—

1. *The granules which constitute the secretion of all varieties of leucocytes are the products of a continuous reaction in the nucleus, in which the nuclein of its nucleus, the materials ingested by the cell, and the plasmatic adrenoxidase, thyroiodase, and alkaline salts take part.*

2. *When a leucocyte becomes functionally incompetent it is destroyed by proteolysis in the blood-plasma.*

CLASSIFICATION OF LEUCOCYTES.—I have proceeded as far as I could with our analysis of the leucocytes as a unit, and it now becomes necessary to ascertain, if possible, the functions of the various types which histologists, headed by Ehrlich, have established with the aid of staining methods.

⁴⁹ Metchnikoff: *Loc. cit.*, p. 115.

Kanthack and Hardy⁵⁰ not only give a clear, though succinct, outline of the various varieties of cells, but they emphasize features of the problem which are of special interest to us. After briefly reviewing the more prominent contributions to our knowledge of the subject since Wharton Jones's memoirs, published in 1846, including the investigations of Rindfleisch (1863) and Max Schultze (1865), they write as follows:—

“After Max Schultze, no further advance was made or, indeed, was possible in the histological analysis of the sporadic mesoblast, until Ehrlich, in 1878, furnished a rational basis for the use of staining reagents by his far-reaching discovery that the elective affinity of certain constituents of tissues for particular stains could be referred to two factors: the *chemical* nature of the staining substance employed and—a point too often neglected by workers who have followed his methods—the nature of the medium in which the stain is dissolved.⁵¹ Ehrlich drew particular attention to the granules, the possession of which characterizes various forms of wandering cells. These he divided into five classes, differing either in their special affinity for bases, acid, or neutral dyes, or in size. The α or eosinophile granulation colors *only* with acid dyes; the β granulation colors with both acid and basic dyes (amphophile); the γ granulation colors *only* with basic dyes, and the individual granules are large; the δ granulation colors *only* with basic dyes, but the individual granules are small; and the ϵ granulation colors *only* in neutral dyes.

“The nomenclature of the granules was extended to the cells bearing them. Thus, the various forms of white cells found by Ehrlich in blood were: I. A small cell free from granules, to which the name lymphocyte was given, from the fact that it appears to be developed in lymphoid tissue. This is the small, non-amœboid form of Max Schultze. II. A cell characterized by possessing fine granules and one or several nuclei. This is by far the most numerous form of white blood-corpuscles in mammalia, and was found by Ehrlich to be neutrophile in man, and amphophile in rabbits and guinea-pigs.

⁵⁰ Kanthack and Hardy: *Loc. cit.*, p.

⁵¹ All the italics are my own.

III. The eosinophile cell, or coarsely granular cell of Wharton Jones and Max Schultze. It occurs only in small numbers in the blood of mammalia, but is abundant in the blood of lower vertebrates. IV. A basophile cell with fine basophile granules (δ granulation).

"The mononuclear amœboid cells of Max Schultze are apparently grouped with the neutrophile cells by Ehrlich. In addition to these forms Ehrlich describes a basophile cell with coarse granules (γ granulation), occurring mainly in connective tissues and also in the blood of frogs, but not in the blood of mammals. These he calls 'Mastzellen.' . . .

"From what we have said so far it will be seen that the group of finely granular blood-corpuscles described by Max Schultze includes the amphophile and neutrophile and the finely granular basophile cells of Ehrlich. Since Ehrlich's work no contribution to our knowledge of the morphology of the wandering cells has been made except on points of detail. Mention must, however, be made of the group of cells recognized by Metchnikoff⁸² in his treatise on inflammation. The term 'leucocyte,' originally applied by the French school of physiologists, is used to designate wandering cells, and the following varieties are recognized: (I) lymphocytes; (II) mononuclear leucocytes with abundant protoplasm and a round nucleus; (III) polynuclear leucocytes, or 'leucocytes neutrophiles'; (IV) eosinophile leucocytes."

My purpose being to ascertain the physiological functions of the various types, Ehrlich's four classes, by affording definite microchemical limits, will probably prove more useful than the simplified groupings that other histologists have introduced, and which, by reducing the number of divisions, have tended to efface landmarks that can serve as clues for research. I will preserve, therefore, Ehrlich's classification, and try to ascertain whether the various types of cell do not differ physiologically from one another as they do histologically.

LYMPHOCYTES AND HYALINE CELLS.—The first cell of the Ehrlich series, the lymphocyte, seems fully entitled to the position accorded it by histologists in general: that of a leucocyte in process of development. The cellular substance is

⁸² Metchnikoff: *Loc. cit.*

devoid of canaliculi (or mitoma) and of granules, although the nucleus itself is supplied with both, and is evidently functionally active. Lymphocytes are considerably smaller (6 to 6.5 μ) than leucocytes, and represents less than one-fourth of the total number of these cells. They are devoid of amœboid motion. Hyaline cells have been classed in the same category, the cell-body being likewise free from granules, as shown in Gulland's plate, Fig. 1. Both may become active, however, before complete maturity is reached.

NEUTROPHILE LEUCOCYTES.—These are extremely important members of the leucocyte family, for they represent fully three-fourths of the white cells of the blood, and constitute Metchnikoff's main group of phagocytes. They are termed "neutrophile" by Ehrlich because their granulations stain with both acid and basic dyes. Their reaction to acid dyes is very much less intense, however, than is the case with purely acidophile cells, according to Kanthack and Hardy. Their granules are small as compared to those of other acidophiles. Though termed "polynuclear" leucocytes by Metchnikoff, the masses thought to represent as many nuclei are united by thin bridges, thus constituting a single nucleus. Especially is this likely, since the only other type of cell deemed phagocytic by Metchnikoff is a mononuclear cell. Gulland contends that no shape of nucleus is invariably associated with granules of a special kind. It seems evident, therefore, that the phagocytic cells are only distinguishable by their affinity for alkaline dyes and a slight affinity for acid dyes, and by the concurrence of these histological properties with small granules.

Kanthack and Hardy, who refer to this leucocyte as a "finely granular oxyphile cell," speak of it as follows: "It has a very limited and precise distribution, for, under normal conditions, it is entirely absent from extravascular spaces, and occurs *only in the blood*,⁵³ where it is by far the most numerous corpuscle, forming 20 to 70 per cent. of the total number of white corpuscles. The fluctuation in this percentage is probably due, in the main, to the great periodic variations in the number of lymphocytes present in the blood. Thus, the effect of a meal is to cause a considerable increase in the number of

⁵³ All italics are my own.

lymphocytes in the blood, and, therefore, a fall in the share of the total white corpuscles due to finely granular cells. If this disturbing factor be eliminated," continue these investigators, "and the percentage of the finely granular oxyphile cells be taken of the adult white corpuscle only, this is found to be always very high: in man, 75 to 90 per cent."

Metchnikoff, referring to the phagocytic properties of these cells, writes as follows⁵⁴: "Even outside the organism these amœboid cells readily inglobe a large number of foreign particles with which they may come in contact, and they may often be seen literally crammed with all sorts of granules. Like the amœbæ, they swallow not only inert bodies, such as granules of carmine or other substances that are insoluble in the fluid surrounding the leucocytes, but also a large number of living organisms." This is merely quoted to emphasize the fact that the leucocytes differentiated by Ehrlich from all others by the term "neutrophile" are, irrespective of the form of their nucleus, the wandering cells which Metchnikoff has shown to fulfill the physiological function he has termed "phagocytosis."

THE NEUTROPHILE LEUCOCYTES IN ASSIMILATION.—The property which these cells so strikingly show: *i.e.*, their ability to engulf or rather ingest substances of all kinds, seems to me to suggest that they are intrusted with another rôle in the body: *i.e.*, *its nutrition*. Macallum⁵⁵ observed, in sections of intestines taken from animals first starved, then fed upon a substance containing albuminate of iron, free leucocytes crowded with granules of iron-pigments in the intestine. Some of these cells appeared to pass out through the epithelial cells, while others advanced into the subepithelial elements. Macallum also found them in the venules of the villi, the spleen, etc.

We have just seen the reference of Kanthack and Hardy to the "considerable increase in the number of lymphocytes in the blood, and, therefore, a fall in the share of the total white corpuscles" caused by a meal. Both these two phenomena become normal events instead of a "disturbing factor" if the process of digestion includes the use of a large proportion of adult or fully developed leucocytes to transport various

⁵⁴ Metchnikoff: *Loc. cit.*, p. 115.

⁵⁵ A. B. Macallum: *Journal of Physiology*, vol. xvi, 1894.

materials from the intestinal canal to various parts of the organism. It is evident that under these circumstances the immediate neoformation of lymphocytes, and their rapid growth, as is probably their wont, to the state of mature cells, becomes a *sine qua non* of continued existence.

Overlooking the possibility of such a function, and led by his own hypothesis to ascribe to intracellular processes the presence of food-products in the leucocyte, Metchnikoff⁶⁶ writes: "The digestion of proteid substances by the leucocytes is well shown by the gradual changes that take place in the muscular fibers which have been inglobed by leucocytes in cases of acute muscular atrophy. The presence of *peptone* in leucocytes, which has been so often proved by Hofmeister, is sufficiently accounted for by this fact of intracellular digestion, and need not, therefore, be referred, as done by this author, to an *absorption* by these cells of the *peptone formed in the alimentary canal*." I need hardly observe, however, that, added to the foregoing testimony, Hofmeister's view seems sustained.

Indeed, the process to which the peptones owe their presence within the cell is not difficult to trace, if the latter's mechanical functions, as I have construed them, are taken into account. The presence of peptones within the perinuclear vacuole being an accepted fact (since it is recognized by both investigators), the presence therein of substances from which the peptones are elaborated must be accounted for. Metchnikoff traces these to products of degeneration, as suggested by his comparison, and perhaps to waste-products of digestion. Hofmeister's conception differs only from this in implying a closer or more direct relationship between the leucocytes and the intestinal contents of their host. In other words, while Hofmeister associates leucocytes with the process of digestion, Metchnikoff looks upon them only in the light of scavengers. That phagocytes may fulfill both rôles is obviously suggested not only by their own chemico-physiological characteristics, but also by their itinerary in the system. Both Hofmeister and Metchnikoff are right, therefore, each in his own way.

In his review of the absorption of proteids Stewart⁶⁷

⁶⁶ Metchnikoff: *Loc. cit.*, p. 124.

⁶⁷ Stewart: "Manual of Physiology," 4th ed., 1900.

writes: "Although a certain amount of egg-albumin and other native or slightly altered proteid substances can be absorbed as such by the small, and even by the large, intestine, there can be no doubt that the greater part of the proteids of the food is first changed into proteoses and peptones. But proteoses and peptones are absent from the blood, and, indeed, when injected into the blood they are excreted in the urine. When injected in larger amount they pass also into the lymph, from which they gradually reach the blood again, and are eventually, as before, eliminated by the kidneys. The clear inference is that when absorbed from the alimentary canal they must be changed into one or both of the chief proteids of blood and lymph (serum-albumin and serum-globulin) in their passage through its walls. And it has actually been shown that during digestion of a proteid meal the mucosa of the stomach and intestine contains proteose and peptone, while none is present in the muscular coat or in any other organ. They rapidly disappear from a portion of the mucous membrane kept at a temperature of about 40° C. outside the body; but not if it has been thrown into boiling water immediately after excision, nor even if it has been heated at 60° C. for a few minutes and then kept at 40° C. Now, a temperature of 60° C. does not destroy an unorganized ferment, but kills a *living cell*. The regeneration of the proteose and peptone must, therefore, presumably take place in *cells*, and the only available cells in this locality are those which line the intestine, or the *leucocytes* which wander between them. Accordingly, both have been credited with the power of absorbing and transforming these substances."⁵⁸

If my views concerning the functions of the epithelial cells of the intestines, as submitted in the seventh chapter, are sound, they subserve an entirely different function from that now generally ascribed to them: *i.e.*, that of supplying the intestinal tract with a secretion calculated mainly to asepticize the intestinal contents. On the other hand, I showed that the lymph-follicles, including Peyer's patches, supply leucocytes, formed in the cytogenic area of the follicles (Flemming's central nodule), to the intestinal cavity through the fenestrated

⁵⁸ All italics are my own.

membrane overlying each follicle. As the inquiry did not afford evidence to the effect that all these leucocytes served to insure destruction of pathogenic bacteria, I stated that *some* of them carried out this function. Indeed, there was good ground for this limitation, for I had already referred to the iron-laden leucocytes observed by Macallum and had been led later on to allude to those charged with the return of bilirubin to the circulation. That the leucocytes supplied to the intestinal canal by the cytogenic follicular areas include some—and probably a large proportion—whose functions it is to ingest proteids *with* the iron and bilirubin, then re-enter the intestinal wall by way of the villi, is very likely. To the various agencies thus incorporated in the organism can now be added that referred to by Metchnikoff in the sentence: “The presence of peptones in leucocytes which has been so often proved by Hofmeister.” While this contributes further evidence to show that my conception of the whole process must be poised upon solid premises, it also suggests that leucocytes ingest *proteids*, and not peptones, from the intestinal canal, because peptones are the terminal products of the digestion of proteids.

If leucocytes ingest proteids, these must accumulate in their perinuclear vacuole and find their way into the nuclear canaliculi. These cells being freshly supplied to the intestinal canal from the follicles, the proportion of blood-plasma in them must be limited when, laden with proteids, they enter the venules of the villi to find their way to the portal vein. Even in this vessel they must again find a dearth of adrenoxidase, for we have seen that this channel is essentially venous. We must not lose sight of the fact, however, that potent additions to its contents are obtainable here: the spleno-pancreatic internal secretion, *i.e.*, trypsin, to which the plasma of arterial blood and dextrose may be superadded when the precincts of the hepatic artery, *i.e.*, the hepatic lobules, are reached.

If these cells do take up proteids and other bodies utilized in nutrition or in the building up of various organic structures, their own canaliculi, *i.e.*, those of the cell-substance, must serve as the eliminatory channels. In other words, proteids ingulfed by the leucocyte must be submitted to a process of digestion in the nucleus and its vacuole, and the products be passed out

as granules. *This elevates leucocytes to the rank of glandular organs*, but we must not overlook the fact that glands in general supply their secretion in the form of granules. Referring to the parotid, for instance, Foster speaks of the secretion as "generally in the form of granules" and of the "granules" which in the submaxillary gland "may obscure the nuclei." The granules of the pancreas, of the intestinal epithelial cells, etc., are also familiar examples. Indeed, all these granules only differ from those of leucocytes in being less complicated molecularly and smaller. They seem to me fully to represent a true, cellular secretion.

What is the nature of the neutrophile's secretion, *i.e.*, the composition of its granules? Milroy and Malcolm⁵⁹ state that the finely granular amphophile (or neutrophiles) granules "are usually taken to be proteid in nature," and refer to the fact that Sherrington had suggested that they might be "of nucleoproteid nature": a view which their own researches confirm. Under the action of alcohol kept at boiling-point, neither fine nor coarse oxyphile granules were dissolved; ether also at boiling-point gave similar results. These agents being then used successively, the granules remained practically unaltered: a fact which leads the authors to conclude that the granules *cannot consist of fat or lecithin*. Weak alkaline solution at 115° to 120° C. almost entirely removed the granules from the finely granular cells, "but the most striking feature was the persistence of two structures, the nuclei and the coarse oxyphile granules." Solutions of sodium carbonate ($\frac{1}{2}$ to 1 per cent.), followed by careful washing, almost entirely removed the fine oxyphile granules in from one to sixteen hours, while the coarse ones were left. Oxalic acid (0.4 per cent. in alcohol, then $1\frac{1}{4}$ -per-cent. watery solution) entirely removed the small granules, a few of the coarsely granular oxyphile cells containing pink-stained granules, while others were vacuolated. As a result of these tests (which should be read *in extenso* in the original paper) Milroy and Malcolm write as follows: "The possibility of both types of granules consisting of the same kind of organic matter either *differently bound* or with organic salts attached in such a way as to alter the solubilities is certainly a

⁵⁹ Milroy and Malcolm: *Journal of Physiology*, vol. xxv, 1899.

strong one. That it is not *simply* albumin or globulin appears evident from the comparatively insoluble character of both types of granules, but especially the coarse oxyphile ones. Again, the fact that the fine granules are not only oxyphile, but also basophile, supports the view that they are composed of a *complex proteid substance*.⁶⁰ . . . The concordance of these facts with those previously recorded appears to me conclusive.

Milroy and Malcolm's researches not only seem to me to give neutrophile granules their own identity (though showing a distinct kinship to the larger acidophile granules), but also to emphasize the fact that these minute masses of proteid substance represent the end-result of the intracellular process that occurs during the journey of the leucocytes from the intestinal villus to the general circulation *via* the portal and hepatic vessels.

Is it only in the cells that the reactions which serve to convert proteids into assimilable products occur? The investigations of Milroy and Malcolm will greatly assist us in elucidating this question.

In their first article on the "Metabolism of Nucleins"⁶¹ these investigators say, in the course of a review of the metabolism of the nucleins under physiological conditions: "When nucleins are taken by the mouth, the first change that they undergo in the alimentary tract is a simple solvent one in the stomach, and that only to a very slight degree. They are never split up into their constituents. They are easily broken up, however, by the *pancreatic secretion*⁶² into an organic phosphorus-holding acid (not nucleic acid) and albumose or peptone. The important points to notice are that the phosphorus is still in organic combination, and that neither ortho- nor meta- phosphoric acid is so formed. It is probable that the organic phosphorus-holding acid so formed is similar to thymic acid. It forms soluble compounds with albumose and peptone, and is, in all probability, so absorbed. After absorption the bodies derived from the nucleins cause a well-marked *leucocytosis*, and the excretion of phosphoric acid in the urine is

⁶⁰ The italics are my own.

⁶¹ Milroy and Malcolm: *Journal of Physiology*, vol. xxiii, No. 3, July 26, 1898.

⁶² All italics are my own.

increased. Whether a hypoleucocytosis *always* precedes the hyperleucocytosis is difficult to say. Almost all the writers on this subject have emphasized the fact that, on giving nucleins by the mouth, the phosphoric acid excretion in the urine is increased; but they have omitted to show that this excretion *cannot be accounted for* by the phosphorus taken in the form of nucleins, there being really more phosphorus excreted by the kidneys than was present in the original nucleins."

Again, as a result of a series of experiments, Milroy and Malcolm are led to the following conclusions among others: "1. The digestion products of nuclein-holding tissues, nuclein and nucleic acid, cause, on being absorbed, a temporary leucocytosis, which is accompanied by a rise in the P_2O_5 excretion above that derivable from the absorbed phosphorus. These alterations are especially well marked after giving nucleic acid. 2. The alloxuric bodies are excreted in excess, after nucleic acid has been given, and in all probability also after large doses of nuclein-holding tissues or nucleins, although in our experiments, owing to the small amount of thymus taken, there was no distinct increase. 3. The uric acid excretion after nucleic acid was only slightly, if at all, increased. We were exceedingly anxious to give larger doses of nucleic acid, but were unable to do so because of certain rather disagreeable symptoms (*severe muscular tremors*) which arose after the *larger* quantity had been given."

The augmented phosphoric acid excretion to which the authors refer, and which they state cannot be accounted for by the phosphorus taken in the form of nucleins, has doubtless suggested to the reader as primary cause the increased functional activity of the adrenal system induced by the phosphorus ingested: an interpretation sustained by the presence of severe muscular tremors, "which arose after the larger quantity had been given." Of course, phosphorus here acts like any other toxic as a stimulant, the anterior pituitary body responding to the effects of organic poisons as well as those foreign to the system as a chemical entity.

Still, this involves the necessity of showing that leucocytes are themselves the seat of the enhanced metabolism and the source of the excess of phosphoric acid to which the muscular

tremors are due, in accord with my previous statements to that effect. Again, if, as I have suggested, the granules represent the leucocytic secretion, an excess of granules must occur under the influence of the stimulation of the adrenal system induced. That such is the case is shown by the following casual remark of Stokes and Wegefarth,⁶³ who, as stated, based their studies of the free granules derived from leucocytes upon examinations of blood taken from about five hundred persons: "In perfectly fresh specimens the granules were not numerous, but they seemed somewhat increased in patients who had been taking *tonics* or various alcoholic drinks."

This, in turn, involves a query as to the manner in which the anterior pituitary body becomes primarily stimulated when nucleins are taken in excess, for it would seem that locked up in the perinuclear vacuole of the leucocytes their phosphorus could not influence the adrenal system through the blood-stream. This would doubtless hold were the intracellular process to cease at any time, but, as this must begin as soon as the cells enter the hepatic capillaries, after acquiring therein their adequate supply of adrenoxidase, their normal production of granules must start at once. An inordinate proportion of nucleins in the food soon supplies the blood-stream, through the agency of the cells, with an abnormal quantity of these minute phosphorus-laden bodies. These at first give rise to excessive functional activity, including among other signs the "severe muscular tremors" to which Milroy and Malcolm refer, coupled with an excess of P_2O_5 production. Persisted in, however, the excessive (relative) ingestion of nucleins brings on, as do other toxics, adrenal insufficiency, which, by entailing a reduced production of adrenoxidase and trypsin, upon which the physiologically perfect intracellular reactions mainly depend, correspondingly lowers the efficiency of the cleavage-processes. This means, instead of the physiologically perfect granules which, we have seen, Milroy and Malcolm found to be proteid in nature, an accumulation in the blood of proteid toxalbumins.

In their first paper, the above-mentioned investigators draw attention to the two decomposition products considered "as more or less characteristic signs of the decomposition of the

⁶³ Stokes and Wegefarth: *Loc. cit.*

nucleins, viz.: the alloxur bases and phosphoric acid." If my conception as outlined in the preceding paragraph is justified, these alloxuric bases are products of *inadequate* metabolism, while phosphoric acid is the product of perfect metabolism. Uric acid having likewise been considered as a product of the complete process, a rise of alloxuric excretion cannot occur along with excessive phosphoric acid production. That my conclusion, based mainly on Horbaczewski's work, was warranted, is shown by what Milroy and Malcolm term "points of special importance" as results of a series of experiments, namely: "1. There is no doubt that the P_2O_5 excretion is increased even when very small doses of thymus are given. 2. Relatively, also, the P_2O_5 is increased in proportion to the nitrogen. 3. With the small amount of thymus taken there was practically no appreciable alteration in the excretion of the alloxuric bodies, either absolutely or relatively to the total nitrogen or total P_2O_5 ." All this serves to emphasize another feature of the problem: *i.e.*, that *phosphoric acid is the prototype of uric acid as a product of perfect or physiological intracellular metabolism, and that the phagocytic leucocytes which take up nucleo-proteids from the intestinal food-products are the seat of the reactions through which these bodies are converted into assimilable products.*

Although I have only dwelt so far, as regards the intracellular processes with which nucleo-proteids are concerned, with neutrophile leucocytes, these are not alone the seat of reactions which, normally performed, end in the production of uric and phosphoric acids. Indeed, we have seen that all leucocytes contain nuclein in their "nucleus"—a fitting name under the circumstances, and the physio-chemical process reviewed only typifies that which occurs in all varieties of leucocytes. Wherein the neutrophile cells are distinguishable, however, is in their ability as phagocytes to take up nucleo-proteids from the intestine, and to break them up, by means of the trypsin and adrenoxidase subsequently absorbed by them, into peptone and an organic compound containing phosphorus.

How are the various bodies, the presence of which this suggests, utilized? The presence of pancreatic secretion in the intestine, and of the spleno-pancreatic secretion in the portal

vein, would suggest that the leucocytes must be carriers of carbohydrates: an important question when we consider the leading functional rôle which myosinogen plays in muscular contraction. Dextrose, formed from glycogen, itself in turn a product derived from starches, forms part of a chain of events which would, in a measure, have to occur within the cell itself. That such is the case is suggested by the investigations of Zabolotny,⁶⁴ who found that phagocytes devoured particles of starch-paste and digested them: features which led this investigator to conclude that "the presence of an amylolytic ferment in the phagocytes cannot be doubted." But Zabolotny likewise states that when leucocytes ingest starch they become iodophile. This, as is well known, has been termed by Ranvier and other physiologists the "*glycogen reaction*."

Foster, referring to this question, says: "In the case of many corpuscles, at all events, we have evidence of the presence of a member of the large group of *carbohydrates*, comprising starches and sugars, viz.: the starch-like body *glycogen*. . . . This glycogen may exist in the living corpuscle as glycogen, but it is very apt, after the death of the corpuscle, to become changed by hydration into some form of sugar, such as maltose or dextrose." Indeed, he furnishes us complementary evidence, alluding to the cellular proteids in the following sentence: "One of these proteids is a body either identical with or closely allied to the proteid called *myosin*, which we shall have to study more fully in connection with muscular tissue." I have shown that myosin is the *post-mortem* product of the action of what remains of oxygen in the plasma upon myosinogen, and that this is the cause of *rigor mortis*. Foster says, in this connection: "And we have reasons for thinking that in the living white corpuscle there does exist a body identical with or allied to *myosinogen*, which we may speak of as being in a fluid condition, and which, on the death of the corpuscle, is converted, by a kind of clotting, into myosin, or into an allied body which, being solid, gives the body of the corpuscle a stiffness and rigidity which it did not possess during life." All this seems to me clearly to suggest that these leucocytes, in the light of my

⁶⁴ Zabolotny: Russian Archives of Pathology, April, 1900.

views, supply the muscle-cells of the entire organism with myosinogen.

Still, our analysis alone so far points to the neutrophiles—by far the most numerous leucocytes in the blood-stream—as the ones upon which this great function would devolve. It becomes necessary, therefore, to control this conclusion by showing that excessive muscular exercise, by creating a demand for myosinogen in the cells of all muscles,—skeletal, cardiac, vascular, etc.,—engenders a leucocytosis in which the neutrophiles prevail. The data for this are available in a study of this subject by R. C. Larrabee,⁶⁵ who writes as follows: “The paper is based on a study of the blood of four of the contestants in the Boston Athletic Association’s Marathon race of 1901. This is a road-race of about twenty-five miles (40 kilometers), held each spring. The severity of the contest will be apparent when it is said that the winner—not included in my four—covered the distance in less than two and one-half hours. This is about ten miles an hour, about as fast as an ordinary man rides his bicycle for pleasure. . . . The blood of these four cases [counted by the author, assisted by Dr. W. H. McBain] before the race showed no abnormalities. The percentage of polymorphonuclear neutrophiles may perhaps run a little high, but this is to be expected in active young men in the best possible physical condition. After the race the blood was taken immediately, within five minutes from the actual finish. In every case a leucocytosis was found, varying from 14,400 to 22,200. The differential count showed that the increase was *mainly* in the polymorphonuclear *neutrophiles*.”

That the exciting cause of the leucocytosis was the increase of waste-products which in turn stimulated the adrenal system, hardly needs to be dwelt upon. Vagal influence incited to inordinate activity and controlled the organs charged with the genesis of these particular cells, while the inordinate oxidation processes started by the overactive adrenals in all tissues accounts for the general leucocytosis which the word “*mainly*” implies.

Myosinogen being a member of the globulin group of proteids, the other members of this group should be represented

⁶⁵ R. C. Larrabee: *Journal of Medical Research*, Jan. 1902.

among the cell's products, particularly fibrinogen found in the blood-plasma in association with serum-globulin and serum-albumin. That such is the case is demonstrable. Stewart⁶⁶ alludes to the sources of nucleo-proteid in the following words: "In shed and clotting blood, the only possible sources of nucleo-proteid, so far as we know, are the corpuscles and the blood-plates. The red corpuscles we may at once dismiss, for, although they contain a small amount of nucleo-proteid, not only do they remain intact under ordinary circumstances during coagulation, but there is the strongest evidence, as has already been pointed out, that they do not make any essential contribution to the process. We have left over the leucocytes and the platelets. The latter are said and the former are known to yield *nucleo-proteids* when they are broken up in the laboratory; and it is highly probable that from both, but especially from the white corpuscles, nucleo-proteid is liberated in the first moments after blood is shed, and that this nucleo-proteid *is then changed into fibrin-ferment.*"

The relationship between the cellular nucleo-proteids and fibrin which this quotation suggests finds itself sustained by Ranvier,⁶⁷ who, alluding to the rôle of granules in the formation of fibrin, says: "Free granulations, which we found in the blood besides the red and white corpuscles, are very numerous; they were termed 'elementary vesicles' by Zimmermann. In a preparation of human blood examined after rouleaux of red corpuscles have formed these granulations may easily be observed, two varieties being distinguishable. The first are spherical, small droplets of fat; the others are angular or variable in shape, and appear at first as if they were fragments of white corpuscles, but differ from the latter in not being altered by water. They are *stained by iodine*, but remain colorless in carmine solutions. We will see that these are also the characteristics of fibrin." After reviewing the phenomena that attend coagulation, and exposure by washing of the fibrinous net-work, he says: "When this preparation is examined and magnified four hundred to five hundred diameters, the fibrinous reticulum can be seen distinctly, and is disposed in a very interesting

⁶⁶ Stewart: *Loc. cit.*

⁶⁷ Ranvier: *Loc. cit.*, 213.

manner: From an angular granulation, from 11 to 10 μ in diameter, very tenuous fibrils start divergingly, then subdivide, to unite with other fibrils, in order to form a delicate net-work. The preparation is covered with these small net-works, each of which has its central granulation. . . . The granulations which serve as centers for each diminutive fibrinous reticulum have the same microchemical properties as the fibrils."

A normal deduction which seems to me to impose itself in this connection is that fibrin is to the blood what myosin is to the muscle-cells, *i.e.*, a post-mortem product due to arrest of the oxidation process which during life is insured by the adrenoxidase—the supposed "fibrin-ferment." In other words, it not only becomes probable that *peptones, myosinogen, and fibrinogen are products of the same variety of leucocyte, the neutrophile, and therefore chemically similar when liberated from the latter, but also that fibrinogen subserves the same purpose in the blood that myosinogen does in muscle: i.e., it supplies it with its primary source of functional energy.*

True, the solubility of fibrin differs somewhat from that of myosin, but this is probably due not to a difference in the molecular structure of fibrinogen as against that of myosinogen, but to the influence of the medium in which the granules are dropped by the leucocyte. Indeed, the ashes of fibrin contain a larger proportion of calcium and magnesium phosphate than does myosinogen.

Another conclusion which now seems warranted is that *the neutrophile leucocytes are the agencies which take up proteids in the intestinal canal, and, after submitting them to a process in which various physio-chemical bodies taken up by them in the portal and hepatic systems take part, distribute the products to every part of the organism, including the blood itself.*

Such being the case, the proteids, inclosed in their diminutive carriers, should not be found in the blood of the portal system. Foster writes, in this connection, after referring to the difficulties attending the experimental determination of the path taken by proteids: "Bearing this in mind, we may state that all observers are agreed that peptone is absent from chyle, or at least that its presence cannot be satisfactorily proved. On the other hand, while some observers have succeeded in finding

peptone in the portal blood after food, but not during fasting, many have failed to demonstrate the presence of peptone in the blood either of the portal vein or of the vessels at large, *even after a meal containing large quantities of proteids.*" Again: "If an artificial circulation of blood be kept up in the mesenteric arteries supplying a loop of intestine removed from the body, the loop may be kept alive for some considerable time. During this survival a considerable quantity of peptone placed in the cavity of the loop will disappear: *i.e.*, will be absorbed, but *cannot be recovered from the blood* which is being used for the artificial circulation, and which escapes from the veins after traversing the intestinal capillaries. The disappearance is *not due to any action of the blood itself*, for peptone introduced into the blood before it is driven through the mesenteric arteries in the experiment may be recovered from the blood as it escapes from the mesenteric veins. It would seem as if the peptone were changed before it actually gets from the interior of the intestine into the interior of the capillaries."⁶⁸ Viewed from my standpoint, *the peptones are hidden in the neutrophile leucocytes which the follicles of the segment continue to produce. These cells, after migrating over the serum-bathed (and thus constantly asepticated) epithelial surface, and ingesting their burden, find their way into the villi's venules and thence into the mesenteric channels.*

If the foregoing analysis and the various deductions submitted are sound, the neutrophile leucocytes must fulfill a rôle in the organism commensurate with their relative proportion in the blood-stream. Indeed, the following conclusion appears to me to have been sustained:—

The neutrophile leucocytes, through the intermediary of their granules, the β granulations of Ehrlich, supply (1) the blood and all tissues (excepting the nervous system) their nutritive elements: i.e., peptones; and (2) the muscles and the blood, the compounds from which they obtain their mechanical energy when exposed to the action of the adrenoxidase: i.e., myosinogen and fibrinogen.

EHRlich's EOSINOPHILE LEUCOCYTES.—Metchnikoff does not grant Ehrlich's eosinophiles phagocytic properties, these

⁶⁸ All italics are my own.

cells being unable to inglobe foreign bodies. Again, as emphasized by Ehrlich, the granules of these cells are only stainable with acid dyes, the other varieties either taking only alkaline dyes or simultaneously, as does the neutrophile just reviewed, both acid and alkaline dyes, etc. This marked affinity for acids obviously gives the eosinophile an identity of its own, while its non-phagocytic functions as clearly separate it from the finely granular cell just reviewed, which is essentially phagocytic. Ehrlich's eosinophile is usually considered under the heading of "coarsely granular oxyphile cell."

These cells only represent from 2 to 4 per cent. of all the leucocytes in the blood-stream, but this proportion is rapidly increased during disease. Kanthack and Hardy, in the article previously quoted, describe them as follows: "The coarsely granular oxyphile cell, or eosinophile cell, varies in size in different animals, not only absolutely, but relatively to the dimensions of the other classes of cells. In man it is larger than either the hyaline cell, the finely granular oxyphile cell or the finely granular basophile cell. In the rat, rabbit, and guinea-pig, on the other hand, it is smaller than the largest hyaline cells, but larger than the finely granular oxyphile and basophile cells.

"The *nucleus* is typically an elongated body bent to form a horseshoe. In the rat the arms of the horseshoe are carried so far round that in film preparations the ends often overlap, giving to the nucleus the appearance of a circle with a large hole in the center. Sometimes the nucleus is lobed; but we are inclined to regard this appearance as being largely due to the stresses to which the nucleus is subjected when the cell is dying. In the living cell at rest, when it is spherical, the shape of the nucleus, so far as it can be determined by the disposition of the cell-granules, is a simple horseshoe or crescent. A distinct nuclear net-work is present.

"*Cell-granules*.—The cell-granules are relatively large, spherical, or slightly ovoid bodies, and are sharply marked off from the cell-substance by their *very high refractive index*, which is so great that in fluid preparations the granules have a *brilliant, greenish luster*.⁶⁹ The cell-substance in which they are im-

⁶⁹ All italics other than those of the side headings are my own.

bedded has the appearance of a clear, transparent, structureless jelly. The intensity of the oxyphile reaction of these granules differs in different animals, but is always high. Thus, it is very high in the case of the granules of man, these staining with eosin dissolved in 95 per cent. alcohol. . . . The granules also stain with weak acid dyes, such as Orange G, hamatoxylin, and sodium sulphindigotate. Ehrlich-Biondi's mixture (washed out with 95 per cent. spirit) colors these bodies brown-purple, and the 'neutral' mixture (washed out with water) stains them a very intense purple. Corrosive sublimate increases the oxyphile reaction, as does also heat when applied to the dried film."

Gulland found Heidenhain's iron-hamatoxylin extremely valuable to counteract "the bright refraction of the granules" which "blinds the eye to the presence of the threads" (my canaliculi). The granules are stained opaquely in shades of black and gray. He was thus able to ascertain that the granules varied greatly as to size, the smallest granules lying close to the astrosphere and the larger at the periphery, the arrangement pointed out by Heidenhain and shown in Figs. 10, 12, and 16 of Gulland's plate. In the newt's blood, as already stated, "these cells are markedly amoeboid, and have the habit of throwing out circular pseudopodia, which are often connected to the main part of the cell only by a very delicate thread." Gulland illustrates this feature in Figs. 3 and 6 of his plate, and states that "it is evident that the threads are often broken through and the spherical portion of the cell-body set free, as the blood contains a large number of them." He also refers to the fact that, "when the eosinophile cells are found degenerated in blood or pus examined in the fresh state, the granules are always in the Brownian movement."

In the study of the granules of neutrophile cells I referred to the chemical analysis of Milroy and Malcolm and to various points of dissimilarity between these cells and the coarse oxyphiles now in question. Considered from the standpoint of the latter, these investigations showed that, while neither alcohol nor ether, nor both of these agents used successively, produced alterations in either variety, the failure of the latter process *excluded* the possibility of their consisting of

fat or lecithin. Weak alkaline solutions at about 120° C. caused (a feature referred to by the authors as striking) the removal of practically all the granules of the finely granular cells (the neutrophiles), and "persistence of two structures, the nuclei and the coarse oxyphile granules." Acetic acid in alcoholic solution and oxalic acid caused partial removal of both granules, but "sodium ethylate in alcoholic solution removed the fine oxyphile granules almost completely and only affected the coarse ones to a slight extent."

The authors, while concluding that the granules might also be nucleo-proteid in nature, *i.e.*, similar to those of the neutrophile cells, account for the discrepancies in the results of their analyses by the following argument: "The fact that weak acid solutions dissolve both types of granules at least partially is not against the view that they are nucleo-proteid in nature, because these bodies are more easily soluble in weak acid solutions than almost any other complex proteid. The fact that some granules are undissolved, while others are removed, is probably due to the fact that the former have undergone coagulation, while the latter have been rapidly fixed, although it may be also due to the nature of the salts which are combined with the proteid."

Still, the very high refractive index to which Kanthack and Hardy and Gulland refer is not characteristic of the neutrophile granules, and this seems to me to testify against an absolute functional similarity between them and the granules of the eosinophiles. Indeed, with the plasma as excipient for the adrenoxidase, we can as readily account for the presence of the "brilliant, greenish luster" witnessed by the above authors as we can for the phosphorescence of the photogenic organs of lightning-bugs: *i.e.*, by the simultaneous presence of phosphorus and oxygen. This seems to me to indicate that we are dealing with a nucleo-proteid body, as Milroy and Malcolm contend, but with one richer in phosphorus than that forming the neutrophile granules.

What are the functions of the eosinophile leucocytes in the organism? The high percentage of phosphorus in their granules suggests the possibility of their being lecithin carriers; but we have seen that the investigations of Milroy and Mal-

colm clearly show that this organic body is absent. L. F. Barker,⁷⁰ of Baltimore, noted the presence of iron in the granules of the eosinophile leucocytes,—a point which he thinks may be of some value in determining the significance of the leucocytic granulations,—but we cannot consider them as the cells intrusted with transportation of iron from the intestine, for they are not phagocytic. Indeed, it has now become evident that the neutrophiles are intrusted with this function, for Macallum used albuminate of iron. The intestinal leucocytes of his previously starved animals evidently took this substance up as they would the proteids of their usual food. Barker's observation, however, adds another link to the chain of evidence which unites the eosinophiles to the neutrophiles, for, in addition to being both nucleo-proteid carriers, they now become also iron carriers. By tracing the itinerary of this iron we may, therefore, obtain a clue to the true identity of its cellular host.

The phagocytes seen by Macallum to ingest the albuminate of iron being assimilated to those charged at all times with the duty of selecting proteids from the intestinal foodstuffs, it becomes a question as to where they can part with their iron in order to facilitate its absorption into the hæmoglobin molecule, of which, as is well known, it forms an important constituent. From the intestine the iron is carried to the portal system, thence into the hepatic lobule. It must be here that the phagocytic leucocytes must take part in some process related to the elaboration of hæmoglobin, for we have seen on page 335 that in the spleen the leucocytes are formed *in situ*, pass out into the pulp-channels, take up the iron-pigment (probably that of disorganized red corpuscles), and carry it to the liver. Again, and for reasons which are there given, I was led to conclude (page 339) that bilirubin and iron were used to build up the hæmoglobin in the lobular (hepatic) capillaries. The liver, therefore, seems to receive iron from both directions—intestine and spleen—a normal mechanism when we consider that the liver's blood passes almost directly to the heart, and thence to the lungs.

⁷⁰ L. F. Barker: Johns Hopkins Hospital Bulletin, Oct., 1894.

How do the eosinophile (*non-phagocytic*) leucocytes acquire their iron? We can hardly imagine that when the splenic or intestinal leucocytes reach the hepatic lobule their contents or any part thereof is disgorged to enable another cell to appropriate it. Indeed, there is not the slightest evidence that such a process occurs, although the eosinophile has already been shown to contain not only iron, but also the other main constituents of the neutrophile cell. There exists a physiological process, however, through which the eosinophile can acquire all the attributes of the latter: *i.e.*, by mitosis, a mode of cell-multiplication known to apply to leucocytes and particularly to neutrophiles. Gulland refers to this feature in the following lines: "The cells which one sees dividing or about to divide have generally the appearance of medium-sized hyaline cells, with a relatively large, rounded nucleus and a comparatively small cell-body, in which the mitoma is not easily made out. But there is no doubt that cells with horseshoe-shaped nuclei [the eosinophiles] divide, and that the nuclei may even advance as far as the spirem stage without altering their shape. Cells with more markedly polymorphous nuclei, as, for instance, the *ordinary oxyphile cells*, certainly divide also, but they seem generally to go through a preliminary resting stage in which the polymorphous nucleus returns to the rounded form."

In Gulland's plate, Figs. 3 and 6, which refer to eosinophiles from newt's blood, graphically portray a secondary process through which these cells can subdivide, or rather yield a portion of their substance. In 3, a spherical pseudopod is in the act of being formed; in 6, three similar masses appear, the lowest of which is on the point of being separated by the mother-cell. Referring to the bridges that connect net-works of granules with basophile leucocytes, Gulland remarks: "I have little doubt that when that stage is reached [he associates the phenomenon with a supposed process of degeneration] these bridges are torn across and the granules are actually left behind. This forms an exact parallel to what happens in the *eosinophiles* of the newt's blood."

It thus becomes evident that recognized cytological phenomena sustain the conclusion that *neutrophile leucocytes are*

the parent-cells of eosinophile leucocytes, and that eosinophiles can part with segments of their cell-substance.

But does the process of neutrophilic mitosis actually occur in the liver? M. Duval,⁷¹ in his study of the hæmatopoietic functions of this organ, refers to the proportion of the red to the white corpuscles in the blood of the portal vein as compared to that in the hepatic vein, and writes: "Researches in this connection give as result: 1 white corpuscle to 746 red in the *portal* vein, and 1 white corpuscle to 170 red in the *sub-hepatic* veins. This difference can only be due to a production of white corpuscles in the liver or to a destruction of red corpuscles." That red-corpuscle destruction is a function of the spleen is sustained by the presence "in the spleen-pulp," using Foster's words, of red corpuscles "in various stages of disorganization, some of them lying within the substance of large colorless corpuscles, and, as it were, being eaten by them." The presence of blood-pigments in the liver has been thought to indicate that red corpuscles were destroyed in this organ; we have seen, on the contrary, that it is the seat of a reconstructive process of which hæmoglobin is the product. Though the liver may be a seat of destruction for red-cell fragments, the likelihood that any entire corpuscle leaves the capillaries of the hepatic lobules to penetrate the cells is so remote that it can be left out of question. On the other hand, we have seen that these capillaries are the seat of the more important processes connected with the blood. It seems probable, therefore, that the liver, owing in part to the inordinate temperature of its lobular channels (106° F.; 41.9° C.), is also the seat of the mitotic process.

"At a certain period," write Böhm, Davidoff, and Huber,⁷² "the embryonic blood consists principally of nucleated red cells, which proliferate in the circulation by indirect division. The colorless blood-cells, the development of which is not yet fully understood, appear later. It is possible that they also are elements of the blood-islands, which do not contain any hæmoglobin. In a later period of embryonic life the liver becomes a blood-forming organ. Recent investigations have shown, how-

⁷¹ M. Duval: "Cours de Physiologie," p. 200.

⁷² Böhm, Davidoff, and Huber: *Loc. cit.*, p. 168.

ever, that it does not take a direct part in the formation of the blood, but only serves as an area in which the *blood-corpuscles proliferate* during their slow passage through its vessels. The *blind, sac-like endings of the venous capillaries* seem to be particularly adapted for this purpose, as in them the blood-current stagnates, and it is here that the greater number of blood-cells reveal mitotic figures. The newly formed elements are finally swept away by the blood-stream and enter the general circulation."

Gulland likewise states that the eosinophile cell is derived from the "finely granular acidophile" (the neutrophile), and the latter is itself traced back to the lymphocyte. "The transition-forms between the finely granular and the coarsely granular acidophile cells are seen much more frequently in the bone-marrow than in the blood," says this investigator, "and it seems certain that both from this source and from mitotic division the main source of the eosinophile cells is in the bone-marrow." That there is ample margin for my view that mitosis may occur in the liver is also suggested by the following additional lines: "They must arise *elsewhere*, however, in *abundance*,"⁷³ for Schaffer⁷⁴ and I⁷⁵ have shown that they are present in the thymus and in lymphatic glands before either bone or bone-marrow is properly formed at all, and Engel⁷⁶ has seen them in the chick's blood on the fifth day of incubation. In the transition-forms (see Figs. 2, 8, 11) there is little in the general shape of the cell and nucleus to distinguish them from the preceding stage." All the evidence tends to show, therefore, that *the process of mitosis, through which eosinophile leucocytes are formed from neutrophile leucocytes, is carried on in the capillaries of the hepatic lobules, though it can also occur elsewhere in the organism.*

I have referred to the direct path which leucocytes can follow from the liver to the heart and thence to the lungs. If eosinophiles are formed in the liver, therefore, the lungs should show indications of the presence of these leucocytes. Proof that such is actually the case is obtainable with the aid of pathol-

⁷³ The italics are my own.

⁷⁴ Schaffer: Centralbl. für die med. Wissen., 1891.

⁷⁵ Gulland: Journal of Path. and Bacteriol., 1894.

⁷⁶ Engel: Archiv f. mikr. Anat., vol. ixiv, 1894.

ogy: *i.e.*, the significant fact that in several pulmonary diseases eosinophile cells are to be found in the sputum. Teichmüller,⁷⁷ for instance, has not only found this to be the case in pulmonary tuberculosis, but considers an increase of these cells favorable from the standpoint of prognosis. In asthma, though a non-ulcerative process is present, eosinophiles are to be found in abundance in the sputum, and Gollasch⁷⁸ states that they are connected with the formation of the Charcot-Leyden crystals. Lenhartz⁷⁹ states that "it is not improbable that the majority of cells designated as 'alveolar epithelia' are variously altered forms of leucocytes. The protoplasm very frequently shows fine or *coarsely granular fatty metamorphosis*, which is characterized by the *strongly refractive index*."

The irregularity of the granules, and the manner in which they form fibrin, as described by Ranvier, and the peculiar color of the granules are recalled by the following description of the Charcot-Leyden crystals by Lenhartz: "The Charcot-Leyden crystals are delicate, very sharply pointed octahedra which occur in very variable size. They present a sometimes water-clear, transparent, sometimes a slightly yellowish-green, Rhine-wine color; they occur either isolated or in dense collections which here and there are jumbled together, or in uniform rows, following the mucous shreds." The same author also says: "The crystals were first found in the sputum by Friedreich in croupous bronchitis. On the other hand, Leyden has drawn attention to their frequent occurrence in asthmatic expectoration."

The association with various pulmonary diseases obviously suggests that their presence is pathological, whereas we consider their presence in the lung as normal, and their *elimination* in their recognizable form as an accompaniment of the morbid state. That such is the case is shown by the fact emphasized by Lenhartz that: "The longer the asthmatic subject is *free from* paroxysms,—that is, the more time allowed for the formation of the crystals,—the more densely the spirals are studded with these crystals."

⁷⁷ Teichmüller: Lenhartz's "Manual of Clinical Microscopy," translation by H. T. Brooks, 1902.

⁷⁸ Gollasch: Fortschritte der Med., vol. 1889.

⁷⁹ Lenhartz: *Loc. cit.*

While all these facts sustain my opinion that the lungs show ample evidence of the presence in them of eosinophile cells and of their granules, their identity as offsprings of the neutrophiles should be demonstrable here, as elsewhere, through their chemical properties. Indeed, their identity as daughter-cells of neutrophile leucocytes does not disappear even in the lungs, for both acids and alkalies can dissolve them, while the test common to both neutrophile and eosinophile granules, *i.e.*, insolubility in alcohol, is also applicable here. Lenhartz not only confirms this assertion by saying, in reference to the crystals: "They are readily dissolved in warm water, acids, and alkalies, but are *insoluble*⁸⁰ in alcohol"; but we also, it seems to me, can consider, as confirmation of my interpretation of the identity of the granules from which the crystals were derived, his statement that: "fixation of the air-dried preparation for one hour in absolute alcohol and subsequent staining with Chenzinsky's *eosin-methylene-blue* solution also gives very good results."

All these facts further confirm the origin of the eosinophile leucocytes from the liver, for there is no other path that would have brought them to the lungs. They also seem to me to indicate that, *after their formation by mitosis in the liver, eosinophile leucocytes are carried to the pulmonary lobules.*

This question has already engaged the attention of pathologists, including Virchow, Wagner, and Cohnheim. Lenhartz's view is fully sustained by my own investigations, however, when he says: "It is not improbable that the majority of the cells designated as '*alveolar epithelia*' are variously altered forms of leucocytes. The protoplasm very frequently shows *fine* or *coarsely* granular fatty metamorphosis, and is characterized by the strongly *refractive index*." Again, while Lenhartz expresses his belief that the positive identification of the "*alveolar epithelia*" is "extremely difficult," he states that he understands thereby "the large oval or round polygonal cells, three to six times as large as a white blood-corpuscle, which are found in almost every sputum. The usually large cell-body is *coarsely granular*, and contains one or several vesicle-like nuclei." The true identity of epithelium of the

⁸⁰ These italics are Dr. Lenhartz's.

alveoli and, therefore, of the lobule of which they form part now seems clear, if interpreted in the light of the data I have submitted: The cells to which Lenhartz refers, *i.e.*, the *lobular epithelial cells*, are aggregates of the *polynuclear neutrophiles* and of the *daughter-cells* of the latter, the *eosinophiles*.

We have seen that the neutrophiles start from the intestinal canal; that Macallum and L. F. Barker found leucocytes gorged with iron in this region, and, finally, that *some* bilirubin at least is recovered from the intestine—obviously, now, by leucocytes. We have traced the latter from the intestinal canal, through the portal system, liver, hepatic veins, heart, thence to the alveoli. After giving the formula of hæmoglobin, Foster writes: "It will thus be seen that hæmoglobin contains, in addition to the other elements usually present in *proteid* substances, a certain amount of *iron*, that is to say, the element iron is a distinct part of the hæmoglobin molecule, a fact which of itself renders hæmoglobin remarkable among the chemical substances present in the animal body." Kanthack and Hardy noted, as previously stated, that "in fluid preparations the granules have a brilliant, greenish luster"—a characteristic of fine hæmoglobin crystals. Hæmoglobin is readily soluble in blood-serum, as are the granules, we have seen. Ether coagulates hæmoglobin; it caused, in Milroy and Malcolm's experiments,⁸¹ the granules to lose a part of their refractive power, even when boiling ether was used. The proteid constituents of the granules of the neutrophiles, myosinogen and fibrinogen, belong to the globulin group.

This recalls my statement in the first edition of this work (p. 441), in respect to the manner in which the heart-muscle was nourished: "Paradoxical as the statement may seem, I was led to conclude that the minute granules referred to on page 433"—a general outline of the prevailing views concerning the histology of the myocardium, in which the minute pigment-granules, easily seen therein microscopically, are mentioned—"were actually supplied to the heart through the intermediary of leucocytes. These cells were found to migrate from the liver (also through the hepatic veins) to the inferior vena cava, where

⁸¹ Milroy and Malcolm: *Loc. cit.*, p. 112.

they meet the adrenal secretion and proceed with it to the right ventricle."

We can now understand how the granules of the neutrophiles are supplied to the muscle-fibers by quoting another of my statements (see page 434) concerning the distribution of fluids in the intimate structure of the heart: "Fluids can penetrate through the maze of cellular tissue to the bare muscular fibers; the sheaths that include the columns or chains of muscular bundles afford a peculiar system of canalization through which the liquids can easily gain access to them. The canals—the lacunæ of Henle—are the intervals *between* the columns of secondary bundles, or their sheaths, rather, which are placed in longitudinal apposition. Schweigger-Seidel and Ranvier having observed that interstitial injections of colored substances penetrated the *lymphatic vessels*, the lacunæ have been considered as adjuncts, or *extensions*, of the latter." In this sense, therefore, the Thebesian channels are adjuncts of the lymphatic system, for it is through their intermediary that the lacunæ of Henle are supplied with myosinogen granules and—a feature I wish to emphasize—their nutritional peptones and their fibrinogen. All of these jointly supply the heart with its working energy, when acted upon by the adrenoxidase of the blood-stream, and, as is the case with all the organs previously reviewed, by the thyriodase also contained in the red corpuscles.

The bulk of the venous blood which enters the heart is sent, we have seen, along with its adrenal secretion and its leucocytes—neutrophile and eosinophile—to the lungs, Virchow, Friedreich, Leyden, Cohnheim, Wagner, Lenhartz, and other investigators having found them in the sputum, and histology having demonstrated their presence in the alveoli. Again, the path for these leucocytes from the intestine to the true respiratory areas of the lungs is comparatively direct: features which distinctly suggest that the protective functions in the respiratory tract resemble those in the intestinal canal, as regards the eosinophilic granules and the phagocytic functions of the neutrophiles, both kinds of cells being present, as we have seen. Of course, the intestinal lymph-follicles being the source of these cells, another arrangement prevails in the pulmonary lobules: *i.e.*, that to which we referred on page 713, to the effect

that the lobular epithelium *per se* is an aggregate of neutrophiles and eosinophiles.

We can readily understand, now, why the eosinophiles deplete themselves of their granules in the alveoli: *i.e.*, to dissolve them in the plasma prior to their absorption by the red corpuscles. Indeed, the reticular structure of red corpuscles, "the same as that of colorless blood-corpuscles,"⁸² observed by Louis Elsberg in 1879, seems to me to present all the features that have led me to consider as canaliculi the threads that constitute this reticulum in the latter cells. That the red-corpuscle "granulations," "platelets," or "hamatoblasts" derived from them are mere droplets of adrenoxidase poured out through these canaliculi is shown by the fact that the characteristic affinity (requiring oxygen and alkaline salts, according to Ehrlich) for methylene-blue again appears: *i.e.*, as manifested by the deep-blue stain which we found in other structures, the axis-cylinder, neuroglia, etc., and in the leucocytes themselves. This fact was also noted by Litten.⁸³ That the droplets pass out through centrifugal channels in the cell, and that the latter presents the general mechanical characteristics of leucocytes, is also suggested by the researches of Hirschfeld,⁸⁴ who observed that the "blood-plates" are first seen as circular disks occupying the center of the cell, then move very slowly toward the periphery, and finally drop out of the cell through a minute aperture, which closes up again. As the "plate" leaves the cell the external portion gradually increases in size and is connected with the rest by a thread. Several of these may leave the cell together from different parts of the periphery. He also found them to stain with methylene-blue and hamatoxylin. It is evident that we have in the red corpuscle a diminutive nucleated sponge capable of absorbing hamoglobin from the serum of the pulmonary alveoli and of dealing it out in the blood-stream as needed by the tissues.

This feature and the functions of the leucocytes just described introduce complementary factors in the respiratory process as I interpreted it in the second chapter. It now seems

⁸² M. L. Holbrook: "Proceedings of the American Microscopical Society," vol. 1894.

⁸³ Litten: *Deutsche med. Wochenschrift*, Nov. 2, 1899.

⁸⁴ Hirschfeld: *Virchow's Archiv*, vol. cxxvi, 1901.

to me that the whole process is summarized in the following conclusions:—

1. *The true respiratory areas in the pulmonary lobules are composed of the alveolar endothelial plates (the non-nucleated epithelium) and groups of eosinophile leucocytes (the nucleated epithelium) interposed between the former.*

2. *The eosinophile cells are the bodies in which hæmoglobin is formed from the proteids, bilirubin, and iron absorbed by their parent-cells, the neutrophiles, in the intestinal canal.*

3. *When the eosinophile leucocytes reach the alveoli from the liver via the heart they assume an orderly arrangement and alter their shape, so as to form the alveolar epithelium.*

4. *The eosinophile leucocytes supply the adjacent plasma with their hæmatin, and the latter is absorbed by the underlying red corpuscles along with the oxygenized secretion (adrenoxi-dase) to form hæmoglobin.*

5. *Leucocytogenesis being governed by the adrenal system, the main factors of the above respiratory process, the production of eosinophile cells and of adrenal secretion, are thus dependent upon the functional integrity of this system.*

6. *The neutrophile leucocytes which accompany the eosinophiles migrate from the capillaries of the pulmonary artery to the perialveolar lymphatics, and supply the interlobular structures with their nutritional and functional elements: i.e., peptones, myosinogen, and fibrinogen.*

7. *During certain diseases neutrophile and basophile leucocytes may also penetrate into the alveoli and be found in the sputum.*

THE BASOPHILE LEUCOCYTES.—These cells show the division into two groups, “finely granular” and “coarsely granular,” which characterizes those just reviewed. They seem to differ from the latter in every other way, however, for, while these are amœboid, basophiles are not considered so by most histologists. Gulland—rightly, in my opinion—contends that they are, the variations of shape that they show and the manner in which they are scattered throughout the body being adduced as main reasons. The nucleus is round, oval, or kidney-like; is less clearly differentiated from the cell-substance,

and stains with much greater difficulty than that of the neutrophile.

As regards their distribution, Ehrlich and Ranvier found them in the peritoneal, pleural, and pericardial cavities, and also in the connective tissue, but, as emphasized by Kanthack and Hardy, the cells in the connective tissue differ somewhat in shape and size from those in the three cavities mentioned. The latter investigators also found the coarsely granular basophiles "exceedingly numerous in connective-tissue spaces, where they form sometimes an almost complete sheath for the *lymph-capillaries*." Their distribution furthermore resembles that of the eosinophiles in the fact that they are relatively very scarce in the blood.

The chemical characteristics of the basophile granules is suggested by a curious phenomenon which is especially noticeable in animals, and to which Kanthack and Hardy refer in the following words: "The unstable, or *explosive*, nature of the coarsely granular basophile cells in certain animals is one of their most remarkable characters. In the rat and mouse perfect preparations of these cells may be very easily made, but in the guinea-pig and rabbit they can be preserved only with the most rapid fixation by heat or absolute alcohol. In these animals the mere exposure of the coelomic fluid to the air, or to contact with a cover-slip for a few seconds, is sufficient to cause their complete disappearance. Cells characterized by great instability have been described elsewhere in *astacus*⁸⁵ as the 'explosive' cell of that animal, and the basophile cells of the guinea-pig and rabbit might, with equal justice, be designated the explosive cells of those animals." A familiar histological fact will suggest the relationship between such a cell and adrenoxidase. Berdal,⁸⁶ quoting Ranvier, says: "The action of oxygen or of the air may be observed in an extremely simple way: A lymph preparation which has served for the examination of amœboid movements is carefully surrounded with paraffin and set aside for thirty-six hours. If, at the end of that time, the lymphatic cells are examined, all will be seen to have reassumed the spherical form and to no longer project

⁸⁵ Hardy: *Journal of Physiology*, Nos. 1 and 2, vol. xiii.

⁸⁶ Berdal: *Loc. cit.*, p. 275.

pseudopodia. Removal of the paraffin and raising of the disk so as to admit a small quantity of air will suffice to cause the amoeboid motion to recur." The explosive nature of the coarsely granular basophile cell can only be due to the one cause: the presence of large proportion of phosphorus, both in its nuclein and granules.

In their paper upon the free granules derived from leucocytes Stokes and Wegfarth review the investigations of H. F. Müller, of Nothnagel's clinic.⁸⁷ This observer found them both in diseased and normal blood, and describes them as "highly refractive, round, or dumb-bell shaped bodies which show a dancing, molecular movement, but no independent motion." When mounted in 1 per cent. osmic acid "the reaction for fat does not occur," nor can they be dissolved by acetic acid or ether. An important feature in connection with our inquiry is that Müller is recorded as stating that "he does not consider them as Ehrlich's neutrophilic granules escaped from leucocytes," and that "the neutrophilic granules are dissolved by dilute acetic acid, while the bodies which he has studied are not dissolved by this acid." This is in perfect accord with the chemical analyses of Milroy and Malcolm, who found that acids dissolved eosinophile granules, and with the observations of Lenhartz in respect to those found in sputum. Stokes and Wegfarth further emphasize the dissimilarity of basophiles from acidophiles in general, as viewed from my standpoint, when they say, doubtless referring to Ranvier's interpretation of the purpose of the granules of white globules: "They are not concerned in the formation of fibrin, since they remain outside of the fibrinous net-work or are only accidentally attached to it." We thus have evidence to the effect that basophiles are different from neutrophiles, both chemically and functionally.

What is the nature of these granules? Müller is stated to disbelieve "that they are true particles of fat, since they do not give a reaction with osmic acid," while he is credited with the opinion "that they may be bodies resembling fat, but which fail to show the osmic acid stain." Indeed, the persistence with which this characteristic appearance is noted by investi-

⁸⁷ H. F. Müller: *Centralbl. für allg. Path. u. path. Anat.*, vol. viii, 1896.

gators is noteworthy. Thus, Kölliker,⁸⁸ Ranvier,⁸⁹ Bizzorero,⁹⁰ von Lünbeck,⁹¹ and Hayem⁹² are referred to by Stokes and Wegefarth as having also observed bodies resembling fat-granules in the blood of normal human beings, those of the last-named investigator and others described by Schiefferdecker and Kossel⁹³ also as fat-granules being thought by Müller to be identical to those observed by him. That they are fat-like, as thought by Müller, but not fat, seems clear.

Müller, we have seen, refers (as do other investigators) to the fact that these granules are "highly refractive." As this sign also attends eosinophilic granules, it would appear to have but little differential value; such is not the case, however, when this property is jointly considered with the osmic acid reaction, for we have here the *two main distinctive signs of myelin*. "It is extremely refringent," writes Berdal, referring to the latter; and he also alludes to the familiar fact that "myelin treated with osmic acid" stains black.

Still, if the granules are composed of myelin, the active constituent of the latter, lecithin, should be present, since we found this body not only in the myelin of nerves, but also in that of the neuron and the interior of the dendrites. That some granules do contain this body is evident, inasmuch as Foster, in his review of the physiological chemistry of white corpuscles, writes: "Next in importance to the proteids as constant constituents of the white cells come certain fats. Among these the most conspicuous is the complex fatty body, *lecithin*." As we now know that the nuclei of all leucocytes are similar in composition, this can only apply to their granules.

This involves the necessity of differentiating between the two kinds of granules present, the acidophiles (neutrophiles and eosinophiles) and basophiles. Foster points to this distinction, it seems to me, when he says: "next in importance to the proteids," etc. The basophilic granules are evidently not composed of nucleo-proteids; a fact which eliminates the acidophile cells and their granules. Indeed, we have confirmatory

⁸⁸ Kölliker: "Handbuch der Gewebelehre des Menschen," 1867.

⁸⁹ Ranvier: "Traité Technique d'Histologie," 1875.

⁹⁰ Bizzorero: "Handbuch der klin. Med.," 1887.

⁹¹ Von Lünbeck: "Grundriss einer klinischen Pathologie des Blutes," 1896.

⁹² Hayem: "Du sang et de ses altérations anatomiques," 1889.

⁹³ Schiefferdecker and Kossel: Gewebelehre, Bd. xi, 1891.

evidence that it is not the latter which contain lecithin in the following allusion to both kinds of acidophile granules by Milroy and Malcolm: "The fact that neither alcohol nor ether dissolves the granules excludes the possibility that they consist of fat or lecithin."

How do basophile cells acquire their lecithin-building constituents? As is well known, emulsified fats also penetrate the intestinal villi, but, instead of entering as do nucleo-proteids into the venules, they enter the lymphatic circulation directly, by way of the lacteals. Are they absorbed by the villi, and then by the lacteals, or are they also taken up by leucocytes and carried into the latter? Inasmuch as the lymph contained in the lymphatic vessels is itself crowded with leucocytes similar to some of those found in the blood-stream, we must first ascertain whether these leucocytes in any way leave the lymphatic circulation in the intestine as they evidently do when the lymph-ducts open into the general venous system at the junction of the internal jugular and the subclavian veins on both sides.

It may prove useful, however, to recall from the start that the so-called "chyme" and "chyle" represent the same liquid, *i.e.*, the lymph, and that these terms were suggested by a temporary *quantitative* difference in the constituents of the lymph in the mesenteric lymphatics, which are greatly increased during the process of absorption. Again, it may also be well to refer to the fact that lymph is merely blood-plasma practically devoid of red corpuscles, but containing lymphocytes and coarsely granular basophile leucocytes, and, besides, minute fat-globules which show an active Brownian movement, though covered with a thin layer of protoplasm to prevent their running together as fat-drops are wont to do.

"Lymph also contains fibrin," writes Mathias Duval, "but a fibrin which is slow to coagulate spontaneously; indeed, lymph removed from the vessel begins, after a quarter of an hour or so, to harden into a colorless jelly, from which a reticulated mass soon becomes separated, as does blood-fibrin undergoing coagulation." The cause of this delay seems to me but a natural result of the absence of both varieties of acidophile leucocytes, while the slow coagulation is but a normal consequence of the

fact that the lymph is plasma which, though derived from the blood, and deprived of neutrophile leucocytes, nevertheless contains more or less fibrinogen. "More or less" is applicable in a double sense here, for lymph taken from the lymphatics of the extremities, for instance, coagulates more rapidly than that taken from some vessels of the trunk. Lymph also contains serum-albumin and serum-globulin in reduced quantity, and relatively very small proportions of urea, neutral fats, and sugar, as compared to the blood. Such is not the case, however, as regards inorganic salts, which are present in the lymph and blood in similar proportions.

What is the nature of the process through which fats are taken up from the intestine and their itinerary in the blood-stream until they are used for the elaboration of basophile granules?

Stewart,⁹⁴ referring to the nature of this process, says: "The common view has long been that the greater part of the fat escapes decomposition, and, after emulsification by the soaps formed from the liberated fatty acids, is absorbed as neutral fat by the epithelial cells covering the villi. If an animal is killed during digestion of a fatty meal, these cells are found to contain globules of different sizes, which stain black with osmic acid, and dissolved out by ether, leaving vacuoles in the cell-substance, and are therefore fat. It has always been difficult to explain how droplets of emulsified fat could get into the interior of the epithelial cells, and yet it certainly passes into them, and not between them." Foster also refers to this feature in the following quotations: "It has, it is true, been maintained by some that they [the neutral fats] pass *between*⁹⁵ the cells, and not into them, but the evidence is distinctly against this view." Alluding to the rods of the striated border, he says: "We may imagine that the globules pass into the cell-substance by help, in some way, of these rods through amœboid movements comparable with the ingestive movements of the body of an amœba; but we have no positive evidence to support this view." . . . "Within the columnar cell, the fat may be seen, both in osmic acid preparations and in fresh living

⁹⁴ Stewart: *Loc. cit.*, p. 370.

⁹⁵ All italics below this word are my own.

cells, to be disposed in globules of various sizes, some large and some small, each globule placed in a space of the protoplasmic cell-substance. It does not follow that the fat actually entered the cell exactly in the form of these *globules*; it may be that the fat passes the striated border in *very* minute spherules, which, reaching the body of the cell, run together into larger globules; but whether this is so or not we do not know."

All this seems pointedly to suggest that the epithelial cells take up minute fat-particles to submit them to some local process. Böhm and von Davidoff⁹⁶ emphasize the feature of the process when they say, referring to the fat-globules in the epithelial cells: "It seemed most probab'le that protoplasmic threads (pseudopodia) were thrown out from each through its *culicular zone*, which, after taking up the fat, withdrew with it again into the cell. But when it was shown that, after feeding with fatty acids or soaps, globules of fats still appeared in the epithelial cells as before, and that the chyle also contained fat, the hypothesis was suggested that the fat is split up by the pancreatic juice into glycerin and fatty acids, and that the fatty acids are then dissolved by the bile and the alkalis of the intestinal juice, only again to combine with the glycerin to form fat *within* the epithelial cells." Stewart further states that "when an animal is fed with fatty acids they are not only absorbed, but appear as neutral fats in the chyle of the thoracic duct, having combined with glycerin in the intestinal wall, and the epithelial cells contain globules of fat, just as they do when the animal is fed with neutral fat." It seems clear, from these and other available data, that *the epithelial cells of the villi capture fat-globules from the intestinal contents and if need be convert this fat into neutral fats.*

We have seen, however, that the villi also take up the leucocytes which ingest proteids. It is important, in this connection, to clearly distinguish the two mechanisms involved one from the other. Böhm and von Davidoff testify to the passage of such cells into the villi by stating: "Leucocytes are sometimes found within the epithelial cells, but more usually between them, and, according to Stöhr, when seen in *these* positions are in *the act* of migrating into the lumen of the in-

⁹⁶ Böhm and von Davidoff: *Loc. cit.*, p. 256.

testine." Stewart, however, remarks, in this connection: "Leucocytes have been asserted to be the active agents in the absorption of fats. They have been described as pushing their way *between* the epithelial cells, fishing, as it were, for fatty particles in the juices of the intestine, and then traveling back to discharge their cargo into the lymph. This view, however, is erroneous." It is erroneous, but only in one respect, in my opinion, *i.e.*, their direct connection with the absorption of fats, for, as stated, the functions of these wandering cells is to carry proteids to the intravillous venules. These do not, therefore, enter the intravillous lacteals. But *other* leucocytes penetrate the latter with the neutral fat-globules. "Although the leucocytes do not aid in the absorption of fat from the *intestine*," says Stewart, "they appear to take it up from the epithelial cells, conveying it through the spaces of the net-work of adenoid tissue that occupies the interior of the villus, to discharge it into the central lacteal, where it mingles with the lymph." The distinction I suggest in this connection appears to me to remove the confusion that exists in the literature of the subject. Briefly, my conception of the process is as follows: *While the leucocytes which ingest proteids from the intestinal foodstuffs pass between the epithelial cells and enter the venules, the leucocytes which ingest fats only carry the latter from the inner limits of the epithelial cells to the interior of the lacteal, and deposit them therein.*

Sir Michael Foster expresses the opinion that the number of leucocytes found to contain any appreciable degree of fat is too small to account for the amount of fat absorbed. But it seems to me that, if these only transfer the fat from the epithelial cells to the lacteals, the to-and-fro excursions of each cell and the enormous number of villi over which the food of a single meal has to pass amply compensate for the apparent paucity of cells. An additional reason adduced by Foster is the fact that the administration of a saline such as magnesium sulphate "produces effects the very reverse of absorption," these cells being present in unusual numbers. As interpreted from my standpoint, and as will be shown when the action of purgatives is studied, these agents greatly increase the flow of serum into the intestinal canal by reflex action and crowd its walls with

defensive agencies, including leucocytes. We are dealing here not with a normal process, such as is the fat-absorbing function, but with an engorgement by protective elements.

The axial contraction and relaxation which occur in the villus to cause its various contents to gravitate into their respective channels may, however, be instrumental in causing fat-particles that have already passed the epithelium to enter not only the lacteal, but the venules also, fat-globules, or what purported to be such, having been found in the blood. This feature and the manner in which fat-globules reach the general lymphatic circulation are exemplified in the following lines by Stewart: "The contraction of the smooth muscular fibers of the villus and the peristaltic movements of the intestinal walls alter the capacity of the lacteal chamber, and so alternately fill it from the lymph of the adenoid reticulum and empty it into the lymphatic vessel with which it is connected. By this kind of pumping action the passage of fat and other substances into the lymphatics is aided. In the dog no fat is absorbed by the blood-vessels, except perhaps a small quantity in the form of soaps; it nearly all goes into the lacteals, and thence by the general lymph-stream through the thoracic duct into the blood."

An interesting feature now asserts itself. Again are all the basophiles poured into a channel, the left subclavian vein, which empties into a large venous trunk, the superior vena cava, which in turn carries them to the right heart. We have practically a repetition of the process witnessed in the case of the neutrophiles with the exception of the passage through the liver, the basophiles being directly transmitted to the heart; and therefore likewise to the pulmonary lobules.

Indeed, my view that the granules of these cells *are* myelin seems confirmed in this connection, for, while Lenhartz alludes to the neutrophilic granules found in colorless sputum, and to the fact that the sputum of asthmatics contains "numerous eosinophile and quite numerous *basophile* leucocytes," he also refers, when reviewing the characteristics of the cells observed microscopically in this connection, to cells that "present considerable coarse granulation," and remarks: "Here, however, the spherules show a decidedly dull appear-

ance, resembling that seen in *crushed nerve-substances*. For this reason they were designated by Virchow as *myelin droplets*." Moreover, Lenhartz⁹⁷ publishes a colored plate, one of the figures of which represents what he terms with E. Wagner "heart-lesion cells" found in the lungs. The granules of these, he says, "are similar to myelin, and, occasionally, *more refringent than fat*."

Evidently the nervous system is supplied with its myelin precisely as the muscles are supplied with their myosinogen. Kanthack and Hardy state that the coarsely granular cells are not only rare, but completely absent from the blood, while the finely granular are relatively rare in the latter except some hours after a meal. "To say that these cells are found in the body only in very small numbers, being confined to the blood and scanty even there," remark these investigators, referring to the finely granular basophiles, "is probably only equivalent to saying that we are at present very ignorant as to their history, distribution, and significance. However, since we find this cell in the blood, but do not find it either in the coelomic fluid or in the interstitial spaces of the tissues (except, perhaps, in those of the mucous coat of the *alimentary canal*), we must, until further facts are forthcoming, regard it as the basophile cell of the blood." Still, they refer to the coarsely granular cells as "occurring only in the extravascular spaces" and in the "interstices of the connective tissue."

It is probable that we have in the finely granular cell the freshly laden cell on its way, when in the blood, to its normal habitat, the connective-tissue spaces, where their granules develop into their normal size. Indeed, Gulland alludes to a basophile cell, represented in one of his plates, of which he says: "The leucocyte was seen to have been fixed in the act of *passing through a narrow hole* between two bundles of connective tissue." This cell is furthermore accompanied by a large number of granules held in a net-work of fibers, which the cell appears to drag along in its travels. It is of this variety of leucocyte that Gulland says: "It has often been remarked that these cells show a great tendency to leave their granules behind them," etc., and the one which, in the portion of this

⁹⁷ Lenhartz: "Mikroskopie und Chemie am Krankenbett," 1900.

section devoted to a review of the general properties of leucocytes, stands pre-eminently as a free-granule producer.

That the cell in migrating from the vessels and passing through connective-tissue interstices has for its purpose to reach the myelin-spaces of nerves is clearly suggested by the manner in which the lymphatic spaces are arranged even in the finer ramifications. "In its course Henle's sheath is not applied against the nerve-tube," writes Berdal⁹⁸; "there is between it and the nerve-tube a space occupied by lymph-plasma which has for its purpose to supply the cylinder-axis with its nutrition." If this statement is interpreted from the standpoint of my views, it is more than nutrition, but myelin-granules, which insinuate themselves—through chemical affinity, doubtless—wherever there is need for them: *i.e.*, wherever their consumption has been greatest. "Medullated nerve-fibers, when examined, frequently present a beaded or varicose appearance," say Pick and Howden⁹⁹; "this is due to manipulation and pressure causing the *oily* matter to collect into drops, and in consequence of the extreme delicacy of the primitive sheath even slight pressure will cause the transudation of fatty matter, which collects in drops of *oil* outside the membrane." Evidently we are not dealing with a fixed mass, but with one made up of extremely mobile particles, which to me, at least, represent as many basophile granules. If the space between Henle's sheath contains lymph supplied with myelin-granules, what is the difference between a nerve thus supplied with its primary source of energy and a "medullated" nerve? None, in my opinion. *Such a nerve as a non-medullated nerve does not exist*, therefore, since a nerve deprived of myelin, if interpreted from my viewpoint, would become a mere plasma-channel.

The pathway to all nerves becomes greatly simplified down to their terminal ramifications, it seems to me, in the presence of Gulland's observation concerning the passage of a basophile leucocyte "through a narrow hole between two bundles of connective tissue." Indeed, "the lymphatic vessels do not exist as distinct channels in the interfascicular connective tissue," says Berdal. "There is no lymphatic vessel in the thickness of the

⁹⁸ Berdal: *Loc. cit.*, p. 152.

⁹⁹ Pick and Howden: *Loc. cit.*, p. 1117.

nervous bundles nor in the sheath surrounding them (Ranvier). The circulation of the lymph in the interior of the bundles is insured by the arrangement of the interfascicular connective tissue, the meshes of which represent lymphatic cavities communicating with the vessels of the interfascicular tissue through *holes* in the lamellar sheaths." On the whole, therefore, it seems to me permissible to conclude that:—

1. *The physiological function of the basophile leucocyte is to convert fats derived from the intestinal foodstuffs into myelin-granules, and to distribute the latter to all parts of the nervous system, including the brain.*

2. *The basophile leucocytes thus supply the entire nervous system with the lecithin-containing compound which combines with the adrenoxidase of the blood-plasma of axis-cylinders, neuroglia fibrils, etc., in the production of nervous energy.*

The different varieties of leucocytes reviewed so far represent, it seems to me, the only three *adult* functional types, the lymphocytes and hyalines being, as stated, immature cells. This does not mean, however, that the latter are functionless; indeed, we have seen that when an active process is initiated these younger cells rapidly increase in the blood and intestinal tract, to replace the large number of their elders that have disappeared to take part in this process. Their development must be extremely rapid, therefore, and their number commensurate with the number of adult leucocytes brought into action, whether this be to distribute (1) the neutrophilic peptones, myosinogen- and fibrinogen- granules, (2) the eosinophilic hæmoglobin granules or (3) the basophilic myelin-granules.

THE FUNCTIONS OF THE LEUCOCYTES IN IMMUNITY.

As the study of the functions of these cells is continued and amplified in the second volume, I will merely incorporate in this section a few brief facts based on the data submitted in the foregoing pages and conclusions based on a study of the subject, which study cannot for want of space be reproduced here.

Metchnikoff terms "phagocyte" any cell deprived of a cellular membrane and capable of incorporating bacteria and other

substances, and of disintegrating them. In the blood, certain leucocytes, particularly the mobile or wandering neutrophilic or polymorphonuclear forms (the "microphages"), the fixed

EXPLANATION OF PLATE.—Fig. 1.—Pfeiffer's phenomenon occurring in the exudation taken from an untouched guinea-pig, the exudation having been withdrawn ten minutes after the injection of 1 cubic centimeter of bouillon containing one loopful of a culture of Constantinople cholera and 0.04 cubic centimeter of preventive serum (of the strength of $\frac{1}{8}$ milligramme). Staining with methylene-blue. *l*, Lymphocytes. Ocular 3. $\frac{1}{18}$ Zeiss.

Fig. 2.—Mass of granules placed around a collection of leucocytes. Exudation of a guinea-pig withdrawn nine minutes after the injection of 1 cubic centimeter of bouillon to which had been added a third of a culture of Oriental-Prussia cholera and 0.04 cubic centimeter of preventive cholera serum of goat (strength, 0.0002). Ocular 2. D. Zeiss.

Fig. 3.—Granular leucocyte surrounded by a zone of vibrionic granules. The exudation was withdrawn twenty-five minutes after the peritoneal injection of one-tenth of an agar-agar culture of Massowah vibrio. Ocular 2. $\frac{1}{18}$ Zeiss.

Fig. 4.—Two mononuclear leucocytes surrounded by granules; a lymphocyte (*l*) and a red blood-corpuscle (*h*) from the same exudation. Same power.

Fig. 5.—The same cells after remaining for three and one-half hours at 26°.

Fig. 6.—Five polynuclear leucocytes from the exudation withdrawn four minutes after the injection into the peritoneum of a guinea-pig (highly vaccinated and prepared with 3 cubic centimeters of bouillon) of 1 cubic centimeter of bouillon with one-third of an agar-agar culture of Oriental-Prussia cholera. *n*, Nucleus of a crushed macrophage. Staining with methylene-blue. Ocular 3. $\frac{1}{18}$ Zeiss.

Fig. 7.—Mononuclear leucocyte filled with Courbevoile cholera vibrios. Peritoneal exudation of a guinea-pig. Ocular 3. $\frac{1}{18}$ Zeiss.

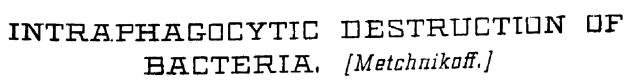
Figs. 8 and 9.—Two polynuclear leucocytes from the same exudation. The vibrios stained gray in the plate are vibrios in the eosinophile stage. Ocular 3. $\frac{1}{18}$ Zeiss.

Figs. 10 to 14.—Various phases in the formation of cultures of cholera vibrio (Oriental Prussia) within leucocytes. Hanging drop, stained with methylene-blue, of the exudation of a guinea-pig hypervaccinated for almost six months and prepared with 3 cubic centimeters of bouillon. The exudation was withdrawn four minutes after the peritoneal injection of one-third of an agar-agar cholera culture placed in 1 cubic centimeter of bouillon and kept at 38°. Ocular 3. $\frac{1}{18}$ Zeiss.

Figs. 15 to 18.—Various phases in the formation of cultures of the Kiel red bacillus within leucocytes. The hanging drop was kept for twenty hours at 17° and was made with the exudation from an hypervaccinated guinea-pig prepared with an injection of 3 cubic centimeters of bouillon. The exudation was withdrawn four minutes after the introduction into the peritoneum of the Kiel bacilli. Ocular 3. $\frac{1}{18}$ Zeiss.

Figs. 19 and 20.—Two consecutive phases of a culture of Kiel red bacilli grown from within a polynuclear leucocyte in a hanging drop of peritoneal exudation. The drop was prepared from the exudation of an hypervaccinated guinea-pig, withdrawn three hours and fifty minutes after the injection of Kiel bacilli into the peritoneum. *n*, Nucleus. Ocular 2. $\frac{1}{18}$ Zeiss.

endothelial and connective-tissue cells, those of the splenic pulp, and the large lymphocytes of the blood ("macrophages") are endowed with this property. Precisely as do the familiar amœbæ, so do these phagocytes ingest bacteria and assimilate them. An



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animal is immune, according to Metchnikoff, as long as its phagocytes freely take up and destroy pathogenic organisms. In proportion, on the other hand, as the functions of the phagocytes are impeded, so is the animal susceptible to disease. That living and dead bacteria are thus disposed of seems to have been satisfactorily shown, while chemotaxis fairly accounts for the affinity which phagocytes show for certain germs in preference to others. Metchnikoff's doctrine as regards the power of certain leucocytes, migrating and fixed, to act as phagocytes is sustained by experimental evidence; the process can easily be followed visually and the leucocytes be seen to ingest micro-organisms, to which they are drawn by chemotactic influence. In 1862 Haeckel witnessed the ingestion of indigo by leucocytes; in 1863 Recklinghausen observed that pus-cells were endowed with amoeboid motion, and, having injected cinnabar grains in the dorsal lymph-sac of frogs, saw that they were engulfed by cells floating in the lymph.

Cohnheim, as long ago as 1867, noted that the smaller vessels of the mesentery became dilated and saw leucocytes range themselves along the vascular walls, plunge their pseudopodia through the mural stomata, and penetrate beyond them, thus migrating and becoming "pus-cells." These pus-cells, in the light of Metchnikoff's theory, are the remains of protective microphages which have succumbed after migrating through vascular walls to meet offensively the pathogenic organism. Dead material, pigment-granules, fragments of tissue, dust-particles, indigo, ivory (in the osseous medullary canal, according to Kölliker), in fact, almost any foreign substance capable of invading the living organic structure, seems to become their prey. An aseptic catgut ligature, a fragment of bacilli-laden tissue, etc., soon becomes coated with an exudate filled with leucocytes which first engulf the bacilli and then the disintegrated tissue. Let any inhibiting cause appear, however,—an excessively virulent germ, an abnormally high temperature, for instance,—their powers cease, and at once the bacilli multiply, causing death of the animal used for the experiment. The rapidity of multiplication of pathogenic organisms is an additional factor operating against successful phagocytic action. When such is the case the phagocytes are themselves destroyed.

Successful phagocytes may be traced from their working field by staining the latter, as was done by Rosenberger; long lines of colored cells may then be seen to radiate in various directions from the stained area. The pathogenic germs, once ingulfed, usually cease to multiply, and, either through a toxic action or starvation, soon die and disappear. That organisms are ingested alive Metchnikoff has shown. Spermatozoa, for instance, ingested by macrophages were seen to continue their motile activity until the tail had also been taken up. Begun in 1865 with the digestive epithelium of *Gedemus bilineatus*, the cellular elements of which were shown to digest various extrinsic substances, Metchnikoff's labors developed in 1883 into his present doctrine of phagocytosis, which, notwithstanding much adverse criticism, has maintained its ground.

The rapidity with which the protective process is carried on in cases of general infection is well illustrated by Cantacuzene:¹⁰⁰ "Immediately after injecting anthrax bacteria in a vein of a rabbit's ear," says this author, "the organisms are taken up by phagocytes. At the end of seven minutes in the liver, eight minutes in the lungs, and one hour in the spleen none of the germs are free. Their destruction in the phagocytes is at first very rapid, but soon some of the latter are overcome, and the bacteria, by multiplying within them, cause them to become centers of pullulation. Still, the bacteria that escape from the dead phagocyte are seized by others; but, the number of the former becoming greater as the battle progresses, their protective powers are correspondingly reduced, and the bacteria finally invade the entire blood-stream. In the liver . . . practically all the bacteria are destroyed and digested within a few minutes after the injection. This superiority of the hepatic phagocytes in the fray lasts almost throughout the disease; but the activity of the phagocytes finally decreases; the bacteria multiply within them and become generalized. In the lungs there is rapid destruction of bacteria by polynuclear cells, then intracellular development of bacteria and generalization."

The phagocytes just referred to, the microphages, are wandering or migrating cells—free to respond and travel more

¹⁰⁰ Cantacuzene: Quoted by Marcel Monnier: *Gazette médicale Belge*, July 13, 1899.

or less promptly toward pathogenic bacteria, in virtue of the chemotactic attraction possessed by the latter. The process is graphically illustrated in the annexed colored plate.

What is the nature of the intraphagocytic process?

I have shown that the germicidal phagocytes, the neutrophiles, absorbed trypsin not only in the intestinal canal while ingulphing foodstuffs, but likewise in the portal vein, the ferment in the latter being, from my viewpoint, the splenopancreatic secretion. This intraphagocytic trypsin is capable of digesting not only certain poisons: toxic albuminoids, toxins, vegetable poisons, venoms, and even drugs, as will be shown in the second volume, but also bacteria. In other words, all materials, poisons, germs, etc., find their doom in the digestive vacuoles of the phagocyte. "Just as amœbæ digest their prey with the aid of amibodiastase, a soluble ferment belonging to the group of the trypsins," writes Metchnikoff, "white corpuscles submit the foreign bodies they inglobe to the action of cytases. These cytases (the alexins or *complements* of other authors) are the soluble ferments which also belong to the category of *trypsins*."¹⁰¹ The two italicized¹⁰² words should be carefully noted, as they indicate that the antibody Ehrlich has termed "complement" is Metchnikoff's "trypsin." As shown in the second volume, this is confirmed from various directions.

As to the rôle of this cytase or trypsin-like body, it is also clearly defined in another sentence by Metchnikoff: "In blood removed from the body the white cells allow plasmane, which causes coagulation of fibrin and the formation of the clot, to pass into the liquid. But at the same time these abandon a portion of their cytase, which communicates to the serum its *hamolytic* and *bactericidal* qualities." Briefly, when bacteria are ingested by phagocytes or phagocytic cells of any kind (for these include the finely granular oxyphiles and the hyaline and giant cells, all wandering cells) they are actually digested in their vacuoles by the trypsin-like cytase precisely as they would be in the alimentary canal of highly organized animals.

It becomes a question now as to *how* the phagocytes become supplied with this trypsin, and how their protective activity to

¹⁰¹ L'Immunité dans les Maladies Infectieuses, p. 573, 1901. See vol. II, p. 907, for additional evidence.

¹⁰² The italics are my own.

the system at large is awakened. Considered from my viewpoint, *i.e.*, with the structure and functions of leucocytes, as described in the foregoing sections, those cells which are phagocytic are influenced in the following manner, when pathogenic bacteria, their toxins, toxic albuminoids, etc., provoke an auto-protective reaction in the body:—

Stimulation of the adreno-thyroid center by the toxic increases the production of adrenoxidase and thyriodase, which in turn enhance correspondingly oxidation and, thereby, the functional activity of all tissues. Among these tissues are (1) those which produce phagocytes (lymphatic structures mainly), thus causing leucocytosis, and also (2) the spleen and pancreas, which jointly (from my viewpoint) produce Metchnikoff's trypsin-like cytase (Ehrlich's complement). This substance, being secreted (as an internal secretion, see p. 367) into the splenic and portal veins, is taken up therein by the newly created phagocytes and stored in their perinuclear vacuole,—their stomach, so to say. The cells, after traversing the liver, penetrate into the general circulation and carry on therein their function of scavengers, *i.e.*, that of ingesting and digesting the pathogenic substance or the bacteria whose toxin had excited the adreno-thyroid center—the sentinel whose mission was to start the defensive reaction.

How Bacterins (Vaccines) Act and how Opsonins Enhance Phagocytosis.—We have seen that in 1907 I advanced the view that the thyro-parathyroid secretion corresponded in its chemical, physiological, and clinical properties with Wright's opsonins, and that the labors of Marbé, Malvoz, and Stepanoff have sustained me. I have also submitted evidence to the effect that it was by increasing the sensitiveness of the *phosphorus* of all cells, and particularly their nuclei, to the oxidizing action of the adrenoxidase that functional activity was enhanced. We have now seen that leucocytes, including the phagocytes, are supplied, like other cells, with a nucleus rich in phosphorus. When, therefore, an excess of thyro-parathyroid secretion, *i.e.*, opsonin, appears in the blood, through the above-described mechanism, and through the red corpuscles, the phagocytes become unusually active and aggressive.

Simultaneously, the pathogenic organisms themselves

undergo a process which renders them vulnerable to the phagocytic host. The thyroparathyroid secretion, we have seen, powerfully excites metabolism, but particularly the catabolic phase of the process; hence its potent action in the reduction of obesity; it influences bacteria precisely as it does adipose tissue, and with especial activity those that are rich in phosphorus, the tubercle bacillus, for example. It renders the germ more vulnerable to digestion by the trypsin of the phagocyte. This effect on them modifies the surface of the germs, softens it and causes them to adhere together, *i.e.*, to agglutinate.

This suggests that opsonin and *agglutinin* are one and the same thing. That such is the case is shown by many experimental facts. We have seen that the thyroparathyroid secretion, which is the opsonin, and the adrenoxidase are contained in the red corpuscles; Nolf¹⁰³ noted that the addition of red corpuscles to serum gave it agglutinating properties. Indeed, Arthur Klein¹⁰⁴ found that agglutinin could be dissolved out of the red corpuscles by means of salt solution or distilled water. It will be recalled that I traced the thyroparathyroid secretion, *i.e.*, the opsonin, to the lungs; Ruffer and Crendiropoulo,¹⁰⁵ in a study of agglutinins, remark: "Strangely enough the lungs of immunized guinea-pigs were the only organs which in the majority of cases possessed agglutinating properties greater than the serum." As is well known, Bordet's "sensibilisatrice" is derived from the red corpuscles; now, Savtchenko¹⁰⁶ has pointed out that this substance was endowed with specific opsonic properties, acting both on bacteria and on leucocytes, as I explained above. Finally, agglutination is evidently a feature of opsonins. Bulloch and Atkins,¹⁰⁷ for example, were led experimentally to conclude that opsonins were "simple substances resembling agglutinins."

This involves the necessity on the part of the opsonin of leaving the red corpuscle to influence morbidly the bacteria. Nolf¹⁰⁸ showed that this was due to an action of the complement (the phagocytic trypsinic cytase) on the red corpuscles which

¹⁰³ Nolf: *Ann. de l'Inst. Pasteur*, xiv, p. 297, 1900.

¹⁰⁴ Arthur Klein: *Wiener klin. Woch.*, Apr. 17, 1902.

¹⁰⁵ Ruffer and Crendiropoulo: *British Medical Journal*, Apr. 5, 1902.

¹⁰⁶ Savtchenko: *Annales de l'Inst. Pasteur*, xvi, p. 106, 1902.

¹⁰⁷ Bulloch and Atkins: *Proc. Royal Soc. of London*, lxxiv, p. 379.

¹⁰⁸ Nolf: *Annales de l'Inst. Pasteur*, xiv, pp. 297, 492, 1900.

caused "the contents of the latter to leave them," and that "the injection of the corpuscular contents incited hæmolysis." In other words, the trypsin of the phagocytes being secreted into the blood, it causes the red corpuscles to secrete their opsonin (with the adrenoxidase—amboceptor), and digestion entailing destruction of the germ can thus occur in the plasma and prove so active, in fact, when there is hyperpyrexia, for example, as to destroy the blood-cells besides, *i.e.*, produce hæmolysis.

The bacteria being softened by the opsonin and rendered more inert, while simultaneously the phagocytes, their enemies, are rendered more active and aggressive, the former are attacked and ingested and they are submitted to digestion in the phagocytic vacuole and destroyed.

On the whole, as viewed from my standpoint, the functions of the leucocytes in general immunity, including Metchnikoff's conception of phagocytosis, may be summarized as follows:—

1. *When bacteria appear in the blood, their toxins—or bacterins or vaccines injected into the tissues which ultimately reach the blood—awaken a defensive reaction in the body at large by exciting the thyro-adrenal center, oxidation and metabolism being increased in all tissues, the production of phagocytes is activated and their aggressiveness is intensified.*

2. *The thyroparathyroid secretion (opsonin and agglutinin) and the adrenoxidase (amboceptor) stored in the red corpuscles are then secreted by these cells under the influence of the phagocytes (Nolf), to sensitize and soften the bacteria.*

3. *The bacteria are then ingested by the phagocytes and digested by their cytase (complement), a trypsin-like ferment, and this process continues as long as there are bacteria to produce toxins capable of exciting the adrenoathyroid center.*

This completes the process as far as the phagocytes are concerned. As their functions are to co-operate with the plasmatic defensive process described under the preceding heading, the nature of this co-operation should also be ascertained. This is described in what I believe to be:—

A SIMPLIFIED THEORY OF IMMUNITY.

There occurs, at first, what might be termed the "preparatory" stage, the purpose of which is to increase the defensive

constituents of the blood and other body fluids. On the whole, it seems permissible to conclude that:—

The toxic (certain toxins, wastes, drugs, vaccines, etc.) excites the immunizing center. This center, in turn, stimulates the thyro-parathyroid glands and adrenals, thus causing them to supply the blood (and to a certain extent the lymph and serous fluids) with an excess of THYROIDASE and ADRENODASE. Metabolism being enhanced in all tissues by these substances, the pancreas also secretes an excess of TRYPSIN FERMENT, while the leucocyto-genic tissues (bone-marrow, lymph-glands, etc.) produce an increased number of leucocytes, mainly FINELY GRANULAR OXYPHILES and PHAGOCYTES.

The blood and other body fluids being now provided with all its defensive agents, the following process is started:—

The thyroiodase (opsonin, agglutinin) sensitizes and softens the pathogenic agent, while the adreno-ridase (amboceptor) oxidizes the phosphorus of the nucleo-proteid granulations, liberating heat; the activity of the trypsin ferments (plasmatic and phagocytic complement) being correspondingly increased the pathogenic agent is converted into benign and eliminable products.*

The whole process imposes protective properties upon each ductless gland involved, i.e., the thyro-parathyroid apparatus, the adrenals and the pituitary. As to the two first named their power to antagonize intoxication is now generally recognized. As to the pituitary body, its rôle in this connection has only, so far, been studied by myself. Suggestive, however, are the remarks of J. A. Flexner,¹⁰⁰ in reference to the after effects of removal of the pituitary for tumor of this organ. "I wish to call attention," writes this observer, "to the extreme susceptibility of these patients to morphine and to auto-intoxication, especially of purin origin." Then, referring to a personal fatal case, he states that "one twenty-fourth of a grain kept her narcotized for over a day," and he rightly concludes that "this sudden and unexpected end was due to stopping of her glandular feedings and to the severe auto-intoxication which resulted from her careless dietary." The rôle I have ascribed to the pituitary body alone explains this phenomenon.

* This relationship of the nucleo-proteid granulations with functional efficiency of the cytase is studied in the second volume, to which the reader is referred.

¹⁰⁰ Flexner: Louisville Monthly Journal of Medicine and Surgery, May, 1912.

CHAPTER XII.

THE INTERNAL SECRETIONS AND ORGANOTHERAPY.

THE FUNDAMENTAL PRINCIPLE OF THE ACTION OF ORGANIC PREPARATIONS.

AMERICAN textbooks afford no clue as to the manner in which the thyroid gland carries on its functions. Some writers hold that the thyroid and parathyroids, by means of an internal secretion, "exercise an important control over the processes of nutrition of the body"; others contend that the purpose of these organs "is to neutralize or destroy toxic substances formed in the metabolism of the rest of the body." Others again assert that it increases metabolic activity, especially catabolism. I have submitted ample evidence to the effect that the thyroid influences all these functions; but *how* does it do so? This is the feature that I have supplied in the present work. If the reader will take into account the fact that the above divers functions, attributed by different groups of investigators to the thyroid, are *all* explained by the one rôle I have attributed to this organ—that of sensitizing the organic phosphorus of all tissues—he will surely concede that my position must be a strong one. And this may be said to apply to the other organs analyzed in this work. The analyses I have submitted have not been destructive; they have proven constructive; they have shown that different sets of experiments and clinical observations which apparently divided several groups of investigators upon each question into as many antagonistic camps were all, when interpreted from my viewpoint, conciliated and harmonized into a consistent whole.

In their application to organotherapy, my views are submitted to a still greater test: they are shown to explain *all* the therapeutic effects of preparations of the organs studied in the present work, namely, the thyroid, parathyroids, adrenals, pituitary, pancreas, spleen, and thymus. Certain organs, such as the kidneys, ovaries, and testicles, whose internal secretions have

not been specifically studied, may be included in the list, for there is some ground for the proposition, at least, that their organic products should not be regarded as special secretions, but as the product of a single kind of secretory cells that are common to many organs, as will be shown below.

If our object to place pharmacology on a scientific footing is ever to be realized, we should insist, whenever an agent is to be tried therapeutically, upon a preliminary determination of its identity as a chemical body. Thus only will it be possible for us to establish its physiological action on a solid basis. In drug therapy, this important feature has been carried out to a considerable extent, and what we know of the physiological action of most agents derived from plant life has been acquired since their active principles have been isolated and made the basis of experimental and clinical study. Just as opium contains various principles—morphine, apomorphine, codeine, etc.—so do animal extracts contain a multiplicity of substances, cellular and plasmatic, and also products of cellular metabolism capable of provoking physiological effects; but here very little effort has been made to isolate the truly useful principles. Hence the confusion and empiricism which has always surrounded the use of these agents.

All this applies to organotherapy as it does to pharmacal agents. It is unquestionably true that we have among the twenty and odd animal extracts that have been proposed a few, at least, which are capable of affording relief where no other class of agent will act—thyroid preparations in myxedema and cretinism, and adrenal extractives in Addison's disease and hemorrhage, for example. The adoption of a systematic line of study in the direction proposed seems to me to facilitate the discovery of additional useful applications of these agents, or, at least, to give their use in practice a more rational basis.

Important in this connection is the identification of the true organotherapeutic preparations. By the "true" agents I mean those which can be used intelligently, that is, with knowledge of the physiological effects produced, because their active principles are known. Thyroid extract belongs to this class, since we know that its action is due to the iodine in organic combination its secretion contains; adrenal preparations like-

wise are included because their active principles, whether epinephrin, suprarenalin or adrenalin, are also known. Conversely, we have a large number of organic preparations that are used blindly, without knowledge of their components, which may number from five to twenty or more, in almost any disease related directly or remotely with the organ from which the extract is obtained. Mammary extract can be cited as an example of these agents. They are hardly entitled to a rank much above that of empirical nostrums until rendered fit, by their sponsors, through chemical, pharmacological, and clinical researches, to be taken up by the profession as legitimate pharmaceutical agents.

That so desirable a task is not impossible of accomplishment may readily be shown. We shall take as examples those which, besides the thyroid, parathyroid, and adrenal products, whose active agents are familiar to every one, the four which have stood out most prominently in the history of opotherapy: the testicular, ovarian, renal, and pituitary extracts.

Spermin, as is well known, is the purest of testicular preparations. Before I had given any attention whatever to these agents, I had submitted evidence¹ which showed that the adrenal secretion was carried to the pulmonary air-cells, to take up the oxygen of the air therein, and become the albuminous (previously unidentified) constituent of the hæmoglobin, which, through the intermediary of the red corpuscles, supplies oxygen to all the tissues. The evidence showed that it was an oxidizing body acting catalytically; that it resisted all temperatures up to, and even, boiling; that it was insoluble in ether and practically insoluble in absolute alcohol, and gave the guaiac, Florence, and other hæmin tests. Now, spermin not only raises the blood-pressure, slows the heart, and produces all other physiological effects peculiar to the adrenal principles, but its solubilities are the same; it gives the same tests; it resists boiling. Moreover, it is regarded in Europe as a powerful "oxidizing tonic" and has been found equally useful in disorders in which adrenal preparations had given good results. The inference that spermin consists mainly of the adrenal product

¹ Sajous: "Internal Secretions and the Principles of Medicine," 1, 1906; 11, 1907.

suggests that it should not be regarded as specific to the testes, but, instead, a constituent of the blood at large; not only did this prove to be the case, but it was found in the blood of females as well as in that of males.

Although ovarian preparations have not been studied as thoroughly, their dependence upon the adrenal principle for their activity is no less evident. Ovarian extract has been found to contain "an oxidizing ferment comparable to spermin."² Just as castration causes a decline of the temperature, so does removal of the ovaries; while both spermin and ovarin restore the temperature to normal. This corresponds with the influence on general oxidation I ascribe to the adrenal secretion. As is the case with the latter, ovarian preparations enhance metabolism and the excretion of phosphoric acid. Again, the resemblance of the physiological effects of ovarian extract to those of adrenal preparations is striking. "Fresh ovarian extract," writes Wilcox,³ "is said, when injected in rabbits, to raise the blood-pressure, diminish the heart's action, and slow the respiration; and when administered to the human female, also to increase the arterial tension. In the castrated animal it is found to increase oxidation to something above the normal degree." Sauv^{3a} states that it increases oxidation and the proportion of hæmoglobin in the blood.

Besides this mutual relationship between the testicular, ovarian and adrenal products, two suggestive facts assert themselves: Not only have Schäfer and others found that a close analogy exists between the interstitial cells of the testicles and ovaries and the corresponding cells of the adrenals, but all three sets of organs are derived from the Wolffian body.

The kidneys have been credited with an internal secretion, but no experimental work so far recorded justifies such a conclusion. There is, however (see page 289), testimony to the effect that, as in the organs just referred to, the adrenal principle is the main active agent. Batty Shaw,⁴ remarking that the favorable effects obtained from renal extracts are similar to those that "have been reported as a result of treatment by

² Batty Shaw: "Organotherapy," 1905.

³ Wilcox: "Pharmacology and Therapeutics," 7th ed., p. 824, 1907.

^{3a} Sauv^{3a}: *Paris médical*, April 1, 1911.

⁴ Batty Shaw: *Loc. cit.*, p. 216, 1905.

means of spermin and testicular extract," suggests that "possibly nephrin and other renal preparations provide a means of stimulating oxidation in general, the kidney merely sharing in this oxidation." The concordance of this opinion with my own view (1903), that the adrenal secretion is the constituent of the hæmoglobin molecule which carries on oxidation, is self-evident. The influence of renal extracts on oxidation is further shown by the observations of Brown-Séquard, Teissier, and Fränkel,⁵ that they increased the output of urea, phosphates, and uric acid, and by those of Brown-Séquard, Dromain, and de Pradel Bra,⁶ Mois,⁷ Bitzou,⁸ Dubois,⁹ and others, which showed that they possessed marked antitoxic power. This also harmonizes with my views, since I have shown, with ample evidence to sustain this assertion, that the adrenal secretion is a basal factor in *all* immunizing processes—as its rôle in oxidation would normally suggest. Even the morbid effects of exaggerated antitoxic activity which I ascribed to excessive doses are exemplified by an observation of Layral's¹⁰ in which renal extract caused death from pernicious anæmia, *i.e.*, from hæmolysis.

Pituitary extracts, we have seen, are active according to which of the two lobes of the pituitary is used to prepare them. Howell, Silvestri, Thaon, and others have found that extracts of the anterior lobe were practically inert, while those of the posterior proved quite active. Howell¹¹ states in this connection that they "cause a marked rise of blood-pressure and slowing of the heart-beat," remarking, moreover, that "these effects resemble in general those obtained from adrenal extracts, but differ in some details." When we take into account the wealth of this organ in nervous elements, deviations in minor effects are readily accounted for.

As previously stated, the adrenal principle is not destroyed by boiling. This was also observed to be the case with extracts of the pituitary lobe, by Schäfer and Herring.¹² These physiologists also noted that they produced dilatation of the renal

⁵ Teissier and Frankel: *Lyon médical*, April 29, 1894.

⁶ Bra: *Comptes-rendus de la Société de Biologie*, July 26, 1895.

⁷ Mois: *Clinica Moderna*, Dec. 1, 1897.

⁸ Bitzou: *Journal de physiologie et de pathologie générale*, Nov. 15, 1901.

⁹ Dubois: *Bulletin général de thérapeutique médicale et chirurgicale*.

¹⁰ Layral: *Bulletin médical*, Oct. 8, 1898.

¹¹ Howell: *Loc. cit.*, 2d ed., p. 802, 1907.

¹² Schäfer and Herring: *Transactions of the Royal Society*, cxix, p. 1, 1906.

vessels, but this is a normal result of the vasoconstriction produced by them in the body at large, owing to the action of the adrenal principle upon the vascular muscles. The renal capillaries, in keeping with all others, being deprived of muscular elements, they are passively dilated by the blood compressed out, as it were, of the larger vessels and the kidneys are dilated.

Herring,¹³ and more recently McCord,^{13a} noted that pituitary extract caused constriction of the peripheral arterioles. This is typical, as is well known, of the action of all adrenal products. As shown by the experiments of Garnier and Thaon,¹⁴ Conti and Curti,¹⁵ and others, the pressor precede the depressor effects. This applies as well to the inhibitory effects on the pancreas recently recorded by Pemberton and Sweet.¹⁶ The mydriatic action of epinephrin, discovered by Meltzer, has also been found by Cramer to apply to pituitary extract. Finally, the clinical effects recorded, especially those on the cardiac disorders by Cyon, Rénon and Delille,¹⁷ clearly indicate that they are due to the adrenal principle pituitary extracts contain. Both are extolled as oxytocics, being deemed far superior to ergot by some. Both also have been found very effective in intestinal paresis. The resemblance of their action to that of adrenal extracts, noted by Schäfer, is explained, therefore; it is to the adrenal principle in the pituitary that extracts of this organ owe their activity. Finally, as shown by Wiesel,¹⁸ the pituitary body is the seat of a large group of chromaffin cells, i.e., adrenal cells, which stain a yellowish or brown color with potassium bichromate.

All these facts seem to me to justify the inclusion of testicular, ovarian, renal, and pituitary extracts in the adrenal group of organic extracts.

I would add that the presence of the adrenal principle throughout the organism is no longer to be doubted. Besides its now-familiar effects on the blood-pressure by a direct action on the blood-vessels, which necessitates its distribution broadcast,

¹³ Herring: *Journal of Physiology*, Nov. 2, 1904.

^{13a} McCord: *Archives of Int. Med.*, Nov. 15, 1911.

¹⁴ Garnier and Thaon: *Journal de physiologie et de pathologie générale*, March, 1906.

¹⁵ Conti and Curti: *Bollettino delle scienze mediche*, Nov., 1906.

¹⁶ Pemberton and Sweet: *Archives of Internal Medicine*, July, 1908.

¹⁷ Rénon and Delille: *Journal des praticiens*, No. 42, 1907.

¹⁸ Wiesel: *International Clinica*, vol. ii, 15th series, 1905.

we have the fact that Mulon found it in the red corpuscles. Even the placental blood contains it. As a conservative pharmacologist, Dixon,¹⁹ wrote, while describing investigations by F. Taylor and himself: "We have shown that the human placenta contains a considerable amount of a substance which is . . . unaffected by boiling. This body has the property of powerfully constricting blood-vessels, of contracting the uterine muscle, of raising the blood-pressure. . . . So far as we have been able to determine, this body has all the properties of adrenalin." Indeed, "adrenalinemia" is now in common use.

The adrenal principle being common to the entire organism, it would seem as if all organic extracts should owe their therapeutic activity to this constituent. But many facts go to show that the proportion of adrenal principle in certain organs—those forming part of the chromaffin system, for example—is far greater than in others, and moreover that they contain cellular elements that are not only similar to the secreting elements of the adrenals, but which are capable of adding to that received from the latter through the blood. This accounts for the fact that removal of the testicles or ovaries lowers the activity of the oxidation processes, though without destroying life itself, as is the case when the adrenals are removed. The obesity which follows removal of the testicles or the ovaries illustrates an effect of this suboxidation.

This does not mean, however, that all organic preparations owe what therapeutic efficiency they have shown mainly to the adrenal principle they contain. The majority of them probably do not. The recent introduction of an oily extract of brain matter seems to have placed the use of this agent on a firmer basis. The phosphorus-laden nucleins derived from brain substance would probably account for what therapeutic value it seems to show. Again, thymus extract has some claim to recognition in disorders which other remedies do not seem to affect. Here again, we have a tissue rich in nuclein, and therefore in phosphorus. May we not have in these and other organic preparations a means of introducing into the body phosphorus so bound up in organic combination that it can be far more readily taken up by our tissues than any prepara-

¹⁹ Dixon: *British Medical Journal*, Sept. 21, 1907.

tion that our laboratories can produce? We must not lose sight of the fact that organotherapy affords, precisely in this direction, possibilities that nothing else in the realm of therapeutics can offer—a statement which applies also to the opportunity they furnish of introducing immunizing bodies directly into the blood—or of compensating for organs whose functions have become inadequate through local disease. But these advantages will only become available when the prevailing empirical use of animal extracts will have been rendered impossible through proper identification of those of their constituents which bring about beneficial effects, the natural precursor to a clear conception of their mode of action.

Another important feature is the distinction of true ductless glands, whose mission is to elaborate a secretion of physiological use to the body at large, from organs which have been credited with such functions on insufficient grounds. Perhaps the habit of requiring considerable evidence from many sources and directions before reaching a conclusion—contrary to the prevailing tendency among experimenters to base a sweeping conclusion upon very few facts—has rendered me too exacting, but I must confess that so far I have not been able to recognize *true* internal secretions in more than three sets of organs, the thyroid, including its glandules, the parathyroids, the adrenals, and the pancreas. In these organs alone has the secretion been identified at the seat of its formation, traced to the bloodstream, and, through the blood, to all tissues. This might be said to apply to the liver, owing to its glycogenic function and to the broadcast distribution of glycogen; but in accord with Claude Bernard's original view, physiologists very properly consider the formation of glycogen as "a temporary reserve supply of carbohydrate material that is laid up in the liver during digestion and is gradually made use of in the intervals between meals."²⁰ Glycogen, therefore, is not a true internal secretion.

Many other organs have been regarded as sources of internal secretions. A close analysis of the question, however, suggests that while the evidence in favor of this view is very meager, many facts tend to disprove it. Investigators who have contended that these and other structures are ductless glands have,

²⁰ Howell: "Textbook of Physiology," p. 735, 1905.

almost without exception, based their contention on the plea that extracts of these structures produce physiological effects. This accounts for the fact that practically every tissue, including muscles, nerves, lymphatic glands, and even ciliary body, nasal mucous membrane, the placenta, has been thought to produce an internal secretion. The weakness of such a plea is self-evident. Almost any organic substance will in some way or other affect the blood-pressure, and when we consider that all tissues contain more or less nuclein, intermediate, and therefore toxic, waste products, red and white corpuscles, and many other substances capable each in its own way of evoking some sort of reaction when injected into animals, the actual value of such experiments is reduced to *nil*. It is about as scientific as the giving of hashed ear for earache.

Finally, and quite in keeping with the above remarks, is that those of the organic products which are to any degree toxic may, through the adrenal system, evoke an auto-protective reaction the symptoms of which seem to the investigator the expression of a physiological function which he credits to the extract used, supposedly an "internal secretion." On the other hand, beneficial effects are sometimes obtained through the fact that certain tissues combine the properties of two or more internal secretions, the posterior pituitary lobe, for instance, which is rich not only in chromaffin or adrenal substance, as stated, but also in nucleins, owing to its wealth in nervous elements.

Some of these physiological effects will be brought out under the remaining headings of this chapter.

THYROID ORGANOTHERAPY.

When, in the light of the data submitted in the third chapter, we administered thyroid gland, which combines the actions of the thyroid and parathyroids, the following effects are produced: It renders the phosphorus of all tissues, and all free substances, such as bacteria, wastes, toxins, etc., containing phosphorus, more inflammable or sensitive to the action of the oxygen in the blood. As this applies particularly to nerves and nerve-centers (all of which are especially rich in phosphorus) the adrenal center and therefore the adrenals themselves are excited, and, the

adrenal secretion being the agent which takes up the oxygen of the air to sustain the blood's oxygenizing power, the supply of oxygen is also increased. All the various phosphorus-laden substances are thus not only rendered more readily oxidizable by thyroid extract, but this remedy also provides indirectly the required oxygen. This is not all, however. As the functions of all organs are enhanced by this process, the pancreas and the leucocytogenic organs are also stimulated, and trypsin and phagocytes, which are the active destroyers of pathogenic organisms, toxins, and other poisons, are also increased. Briefly, under the influence of thyroid preparations, we have in the blood—and demonstrable therein—all the active agents concerned with *metabolism*, *nutrition*, and *immunity*: an increase (1) of adrenal oxidizing substance, or adrenoxidase (the albuminous constituent of hæmoglobin; Ehrlich's amboceptor); (2) of thyroid sensitizing substance (Wright's opsonin); (3) of trypsin (Ehrlich's complement and Metchnikoff's cytase) and (4) bacteriolytic leucocytes (Metchnikoff's phagocytes).

When, therefore, thyroid preparations are given in small doses, we may expect the following phenomena, especially when the remedy is given in cases of hypothyroidia:—

A *rise of temperature* due to the increased oxidation brought about by the thyroid and adrenal oxidizing substances acting jointly; *enhanced metabolism* a normal result of the augmentation of general oxidation, with *increased appetite* due to the resulting greater demand for foodstuffs. A marked improvement in *general nutrition* and *strength* is a self-evident result of the assimilation of a greater proportion of food-materials, and the *rapid growth* likewise where, as in cretinism, it is stunted. The *cerebro-spinal system* is particularly influenced owing to its wealth in phosphorus; there is, in suitable cases, *development of intelligence*. All organs being the seat of increased metabolic activity and nutrition, the intestinal, renal, cardiac, and cutaneous and hepatic functions are all enhanced. Even the hair grows bountifully not only in cretinism, but when its loss is due to impaired nutrition of thyroid origin. It counteracts *premature senility* in all its phases by restoring to the organism the main constituent which sustains, with the co-operation of the adrenoxidase, the functional efficiency of all its parts.

In large doses, on the other hand, thyroid preparations produce quite the opposite effects. By imposing hyperoxidation upon all cells, these are catabolized or broken down before they can be adequately built up, *i.e.*, anabolized, and, instead of increased nutrition, we behold gradual emaciation beginning with the adipose tissues, which are the first to succumb. Hence the use of thyroid preparations in obesity.

Small doses are, therefore, indicated in all cases to begin with, 1 grain (0.066 Gm.) of the desiccated thyroid in adults, for example, and $\frac{1}{2}$ grain (0.033 Gm.) in children over 2 years old. Gradually, the dose may then be increased, remembering that 3 grains (0.2 Gm.) three times daily should not be exceeded—notwithstanding the “average dose” of 4 grains (0.26 Gm.) given in the U. S. P., which is excessive. A milk-sugar triturate termed *iodothylin*, though not as active as the above, is more suitable for little children in 1- to 5- grain doses.

When thyroid preparations are judiciously used, that is to say, when their action is controlled by giving only carefully adjusted doses, aided by the concomitant use, if needed, of other agents—iron, for example—to supply the hæmatin necessary to build up the hæmoglobin molecule; when also with thyroid we wish to increase the albuminous moiety of that molecule, strychnine when the blood-pressure is too low to insure adequate tissue nutrition, etc., results are obtained which soon convince the clinician that they constitute a very valuable addition to our armamentarium. Especially does this obtain:—

1. In diseases due to slowed destruction of toxic wastes, as shown by its action in tetany, epilepsy, eclampsia, disorders of menopause, asthma, chronic rheumatism, migraine, and also by those due to slow oxidation of fats, as in obesity.

2. In diseases due to lowered general nutrition of all tissues, including the bones, as shown by its action in hypothyroidia, cretinism, myxœdema, and kindred disorders in which calcium metabolism obtains—osteomalacia, rickets, and osteomyelitis.

3. In disorders due to lowered nutrition of the muscular elements, including the skeletal and vascular muscles, as shown by its action in general adynamia, neurasthenia, and myasthenia.

4. In all cases in which the processes of repair or absorption are deficient, as shown by its action in delayed union of frac-

tures, certain benign and malignant neoplasms, and syphilitic tissue and bone necrosis.

5. In infectious diseases—owing to the increase of auto-antitoxin, thyroiodase (opsonin), and phagocytes—as shown by its action in the early stages of tuberculosis, typhoid fever, infectious tonsillitis, and certain exanthemata.

The majority of the disorders enumerated above, apart from those already reviewed, will be found treated at length in the second volume. In the following pages, however, I will include only those conditions which in addition to those studied in the third, fourth, and fifth chapters of the present volume, and in the second volume, are of special practical importance as a field for thyroid organotherapy.

INSANITY.—What data we possess on the relations between mental disorders and the thyroid apparatus indicate that both hypothyroidia and hyperthyroidia are equally fruitful in the genesis of many psychoses. Could we clearly establish a line of demarkation between these two states, however, their study would present no difficulty; but such is not the case in the light of prevailing views. Thus the classic symptoms of myxœdema may be accompanied, especially in the advanced stage, by mental disorders which are not in keeping with the asthenic phenomena that belong to hypothyroidia. The report of the Committee of the Clinical Society of London showed, for instance, that, while a certain proportion of cases of myxœdema suffered from melancholia, the one mental disorder we should expect to find in such a depressive state of the thyroid apparatus, the majority suffered from dementia, acute and chronic mania, delusions, and hallucinations, all of which denote some degree of functional erethism.

Nor do we obtain aid through the morbid histology of the thyroid in insane cases. As stated by Ramadier and Marchand,¹ after an examination of 278 thyroid glands of patients who had died in four different asylums, it is impossible to establish any constant relation between the thyroid changes and the form of mental disease from which the patient suffered.

Yet, there is much to be discerned and there are many therapeutic hints to be garnered when these cases are interpreted

¹ Ramadier and Marchand: *L'Encéphale*, Aug., 1908.

from the standpoint of the views defended in the present work. Thus, taking the influence of the thyroparathyroid mechanism upon oxidation and metabolism as factors of the problem, we have in hypothyroidia such mental states as melancholia, hypochondria, and apathetic delusional insanity, with perhaps ideas of suspicion. What mental disorders are witnessed in the more advanced stage of myxœdema are also commonly characterized as melancholia. So marked is the depressive state in these cases, in fact, that the late Lloyd Andreizen² was led to assert that various insanities having a constant and distinct physiognomy grew in the soil of acromegaly and myxœdema. "In the one case (myxœdema)," he wrote, "a morbid process starting from the thyroid gland affected the whole capacity of the blood in regard to its power of taking up oxygen from the air. On examining the blood with the mercurial pump, it was found that its oxygen and carbonic acid were much diminished, and, by placing the individual in the apparatus for examining the gases of respiration, it was found out that he took in but little oxygen and correspondingly gave out but little carbonic acid during life." That this sustains my own view that the thyroid, partly through its influence on the adrenals, influences tissue respiration is obvious. But this, in itself, sustains Andreizen in his conclusion that certain mental disorders grow in the soil of myxœdema. In other words, we should look upon hypothyroidia as one of the causes of depressive mental states.

This, however, fails to account for the opposite phenomena, *i.e.*, those we associate with erethism, mania, dementia, and the various manifestations in which irritability and excitement are prominent. But these signs are also explained by my conception of the functions of the thyroparathyroid apparatus, *i.e.*, that it acts as opsonin to insure the destruction of toxic wastes. Oxidation and metabolism, particularly its catabolic phase, we have seen, being impaired by the existing hypothyroidia, we have an accumulation of toxic wastes in the blood, and it is to the morbid influence of these poisons on the brain that all manifestations, in myxœdema, such as mental excitement, persistent hallucinations or delusions, and mania, must be attributed. Here, again, Andreizen struck the keynote of the problem, in my opin-

² Andreizen: Quoted by Hamilton: Medical Record, April 29, 1899.

ion, when, in his study of the relations of autotoxin in its bearing upon insanity, to which the previous quotation belongs, he referred to the presence with weakness, dullness, and subnormal temperature "of a tendency to the accumulation of incompletely oxidized bodies (fat, etc.)" in the tissues. Correct also, from my viewpoint, were the estimates of Bruce,³ who, in reporting the results of thyroid treatment in 60 cases, attributed the improvement noted to the production, by the remedy, of a febrile state—quite in keeping with my own view (see page 628) that the thyroid and the adrenals are active in the genesis of fever.

Such being the case, we can conceive how myxœdema and hypothyroidia can become the soil not only for depressive mental disorders, but also for those in which excitement and cellular erethism prevail. It follows also that hypothyroidia should be considered as a prominent factor in the genesis of insanity. Having in myxœdema undeniable proof of the influence of the thyroid apparatus on the mental equilibrium and a rational explanation of the pathogenic process, the physiology of these, particularly the important rôle in immunity, should no longer be neglected by psychiatrists. Laignel-Lavastine⁴ closed an able study of this subject by the statement that "the existence of glandular disorders in psychical syndromes has not as yet, in my opinion, attracted sufficient attention. Nevertheless the existence of such disorders in certain cases is undeniable." Frankl Hochwart^{5a} also lays stress upon this connection.

Recently, L. Vernon Briggs⁵ wrote more pointedly, emphasizing both the rôle of autointoxication and the neglect of this important factor in mental disease: "In many large public and private institutions those in charge receive early cases of mental disturbance, and watch the toxæmia verge into mania, catatonia, and dementia; they notice the acetone breath and are aware of the true condition; but little if anything is done to stay the progress of the disease, and to save these individuals."

As to treatment of this class of psychoses, there is good ground for the belief that, intelligently employed in suitable cases, considerable help can be gained from thyroid preparations.

³ Bruce: *Journal of Mental Science*, Oct., 1895.

⁴ Laignel-Lavastine: *La Presse médicale*, Aug. 1, 1908.

^{5a} Frankl Hochwart: *Amer. Jour. of the Medical Sciences*, Aug., 1913.

⁵ L. Vernon Briggs: *Lancet-Clinic*, Jan. 28, 1911.

McLane Hamilton,⁶ who, with Andreizen, attributes various forms of insanity associated with disease of the thyroid gland to autointoxication, refers to his own experience and to that of Babcock,⁷ Clark, and others to the therapeutic value of these agents. In cases of stuporous melancholia, cerebral exhaustion, and chronic disturbed states of an asthenic type, there was a prompt lighting up of the mental condition, elevation of the temperature, and an increase of hæmoglobin in some instances of over 20 per cent. They were also found useful in chronic insanity with erotic delusions and psychoses in which the complete symptom-complex of catatonia was present, and also in cases of climacteric despondency. Easterbrook,⁸ using thyroid in 100 cases which had proved intractable by other methods, obtained 12 per cent. recoveries. He found it more effective in women than in men, the best results being obtained in mental disorders connected with childbearing. Of 22 patients treated by Leeper,⁹ 12 recovered; only 1 of these required readmission subsequently, all others being, as far as he could ascertain, permanently relieved. Conversely, A. W. Wilcox¹⁰ did not obtain satisfactory results. His beginning daily dose was 15 grains (1 Gm.), increased daily by 15 grains (1 Gm.) until 60 grains (4 Gm.) were given daily.

Very valuable in this connection is a report by Mabon and Babcock,¹¹ based on the results of thyroid treatment in 1032 collected cases of insanity, in which the following conclusions are reached: 1. The dose of the extract depends entirely on the individual case. In some cases 25 grains (1.65 Gm.) three times a day will be necessary to bring about a circulatory or temperature reaction, while in others the same results may be had with the use of 5 grains (0.33 Gm.) *t. i. d.* Each case must be a law unto itself. 2. It is essential that the patient should be placed in bed to obtain the best results, and he should be continued there during the entire treatment and for a week following its discontinuance. 3. The treatment should be continued for at least thirty days. 4. We should not be discouraged by failure

⁶ McLane Hamilton: Medical Record, April 29, 1899.

⁷ Babcock: New York State Hospital's Bulletin, Jan., 1896.

⁸ Easterbrook: Scottish Med. and Surg. Jour., Dec., 1900.

⁹ Leeper: Medical Press and Circular, July 5, 1905.

¹⁰ Wilcox: London Lancet, May 20, 1899.

¹¹ Mabon and Babcock: American Journal of Insanity, Oct., 1899.

in the first administration, but should resort to two, three, or more trials, if necessary. 5. The most gratifying results in thyroid treatment are to be obtained in cases of acute mania and melancholia with prolonged attacks, puerperal and climacteric insanities, stuporous states and primary dementia, particularly where these forms of mental alienation do not respond to the usual methods of treatment. 6. A high temperature reaction is not essential, as the average maximum temperature in the recovered cases among men was 99.6° . 7. Physical improvement is the outcome in most cases whether mental improvement takes place or not. 8. The proportion of individuals who recover under thyroid treatment and then relapse is less than the proportion that relapse after recovery from other methods of treatment. In a series of his cases only one patient who had recovered has relapsed.

I would urge in this connection that *small* doses of desiccated thyroid, 1 grain (0.066 Gm.), increased only if necessary to 2 grains (0.13 Gm.) at most, be used in these cases. Those who have criticised the use of thyroid in psychoses erred in this direction and brought on, by excessive doses, the very untoward phenomena which they deplore, by loading the blood with pathogenic wastes.

Hypodermoclysis or enteroclysis should also be used periodically to facilitate osmosis and hasten the elimination of all wastes through kidneys, intestines, and skin.

Again, it should be remembered that—at least according to my views—the use of thyroid gland enhances the vulnerability of the organic phosphorus to oxidation, and that, therefore, the consumption of this element is greatly augmented by this agent, as is well shown by the increased elimination of P_2O_5 . This loss should be compensated for, particularly in depressive mental states (the brain-cells being rich in phosphorus), by administering lecithin, or glycerophosphate. Berkeley,¹² though unaware of my explanation of the influence of thyroid on tissue phosphorus, found lecithin very valuable in catatonia when given in conjunction with small doses of desiccated thyroid.

In dementia præcox we have the opposite condition, *i.e.*, hyperthyroidia as an underlying cause. As Berkeley states:

¹² Berkeley: *Ibid.*, Jan., 1909.

"Exophthalmic goiter cases and cases of catatonic dementia præcox have usually an enlargement of the thyroid gland, the bruit over the neck, the high tension and rather rapid pulse, accentuation of the second aortic sound, wide pupils, increase of the superficial and deep reflexes, and, lastly, a moderately small cell lymphocytosis."¹³ The inference is obvious: excess of thyroid activity must be the underlying cause of dementia præcox. Thyroid and other organic agents proved harmful, but partial removal of the thyroid proved curative, as first shown by Berkley. Yet, as in other forms of insanity, some cases, especially those of the hebephrenic type, have been benefited by thyroid treatment, as observed by Levison,^{13a} Davidson,^{13b} and others. Dercum and Ellis^{13c} found in eight autopsies degenerative changes in the thyroid and adrenals.

EPILEPSY.—There are certain features of the pathogenesis of epilepsy which the average textbook author seems invariably to overlook. Besides the usual array of symptoms, diagnostic points, etc., the well-worn and recognized etiological factors; intestinal worms, indigestible foods, cicatrices, dentition, fright, masturbation, alcohol, lead poisoning, syphilis, uræmia, and that great basket of iniquities, heredity, are doing duty as of old, with tumors, sclerosis, and nuclear degeneration as local lesions. The physician is enjoined to remove the cause in all conditions in which this is at all possible, to look to depressants as mainstays—with the bromides and chloral in the lead—and to think well of asylums and retreats.

The features which seem to be overlooked are peculiar in the sense that, from the standpoint of practice, they exceed all others in importance. In fact, they constitute the *deus ex machina* of the fit, as it were. Literature shows plainly, for instance, that the dominant note in the pathogenesis of the convulsions is impairment of metabolism, and that the spasmogenic agent is some toxic agent in the blood-stream. Pathological variations of vasomotor action, due more or less to a morbid condition of the blood, have also asserted themselves so strikingly in the production of fits that some observers have been inclined to regard

¹³ Berkley: *Loc. cit.*

^{13a} Levison: *Hospitaltidende*, No. 36, 1909.

^{13b} Davidson: *Australasian Med. Gaz.*, April 20, 1911.

^{13c} Dercum and Ellis: *Jour. of Nerv. and Mental Dis.*, Feb., 1913.

them as the foundation of the whole symptom-complex. Again, destruction of the spasmogenic agent has been urged by some as the only reasonable principle of cure in opposition to the use of bromides and chloral, which tend to increase its formation in the blood-stream.

As to the presence of toxic wastes, so able an observer as L. Pierce Clark,¹⁴ after a study of 150,000 seizures, concludes that "we must see the principle of pathogenesis in an initial toxin or auto-intoxication," i.e., "an accumulation of waste products." The relationship between the latter and the production of epileptic seizures is further shown by the fact, emphasized by Van Gieson¹⁵ and many others, that the attacks are more frequent when gastro-intestinal disorders, especially those due to over-eating, gulping, and constipation, are present than at other times. Indeed, Herter¹⁶ caused typical tonic and clonic convulsions and death in rabbits in forty-five minutes by injecting the defibrinated blood of an epileptic overfeeder, while blood from an ordinary patient did not produce such effects. Krainsky¹⁷ also provoked characteristic seizures in rabbits in two or three minutes and several recurrences with blood-serum obtained by cupping from a case in status epilepticus. Ceni¹⁸ found the blood of epileptics poisonous to man also. Thus, he ascertained experimentally that "non-epileptic subjects react under injections of hypertoxic serum, and present intoxication phenomena that are analogous to those observed in epileptics, though less intense and unaccompanied with psychic disorders or epileptic attacks."

The effect of such poisons on the *vasomotor mechanism* is quite as evident. The conjunctiva and face of the epileptic from whom Herter obtained the hypertoxic serum referred to were congested. That this was due to the action of the poison in his blood is shown by many facts. "Certain drugs, notably absinthé," writes Schäfer,¹⁹ "produce, when injected into the vascular system, convulsive attacks which are scarcely distinguishable from the epileptic fits provoked by stimulation of the cortex cerebri." Now, all such drugs cause a marked rise of the blood-

¹⁴ L. Pierce Clark: *Medical News*, July 18, 1903.

¹⁵ Van Gieson: Cited by House: *Buffalo Medical Journal*, June, 1898.

¹⁶ Herter: *Jour. of Nerv. and Ment. Dis.*, Feb., 1899.

¹⁷ Krainsky: *Wiener klin. Woch.*, Feb. 24, 1898.

¹⁸ Ceni: *Rivista Sperimentale di Freniatria*, vol. xxxi, Fasc. II, 1905.

¹⁹ Schäfer: "*T. B. of Physiol.*," vol. II, p. 721, 1900.

pressure. This may be shown by comparison with a few of the many other spasmogenic drugs. Thus, while absinthe was found to cause intense congestion of all organs examined by Pauly and Bonne,²⁰ Wood²¹ states that "the full dose of strychnine produces a rise of the arterial pressure which is enormously increased during the convulsions." He refers also to the observation of Bezold and Bloebaum, "that when a small dose of atropine is injected into the carotid artery near the vasomotor centers" . . . "there is an instantaneous rise of blood-pressure"—"a great rise," he subsequently remarks. Cocaine, as shown by von Anrep, causes "convulsive movements of cerebral origin" which "are arrested by section of the spinal cord." Wood also says: "Certainly the evidence is overwhelming that cocaine directly increases the blood-pressure." The fits caused by this drug are precisely those of epilepsy; the syndrome is known, in fact, as "cocaine epilepsy."

In typical epilepsy the participation of the vasomotor mechanism is none the less marked. Spitzka, over thirty years ago (1881), attributed the epileptic seizures to the "explosive activity of an unduly irritable vasomotor center," and most neurologists regard epilepsy as "a functional vasomotor disease." The blood-pressure is not only high, as observed by François-Franck and Pitres, but the speed of the blood-stream in muscular vessels, according to Leonard Hill,²² is from three to five times greater than usual—an index of the violence of the cortical circulation. Indeed, Weber²³ found vascular lesions and extravasations in the cortex and medulla of cases of status epilepticus, so great was the force which urged the blood into the capillaries. Onuf even found, besides the capillary changes, tortuosity and aneurismal dilatations. Victor Horsley²⁴ has emphasized the importance of congestion of the cortical mantle in the production of epileptic seizures. Ito²⁵ caused them in guinea-pigs by producing traumatic hyperæmia of the cortex.

We thus have, as cause of the convulsions, a toxic in the blood capable of producing a high vascular tension, and thereby

²⁰ Pauly and Bonne: *Gaz. hebdomadaire de médecine et de chirurgie*, May 13, 1897.

²¹ Wood: "Therapeutics, Its Principles and Practice," 13th ed., p. 217, 1906.

²² Leonard Hill: Schäfer's "T. B. of Physiol.," vol. II, p. 155, 1898.

²³ Weber: *Wiener med. Wochenschrift*, Bd. XLIX, S. 158, 1899.

²⁴ Victor Horsley: *British Medical Journal*, April 2, 1892.

²⁵ Ito: *Deut. Zeit. f. Chir.*, Aug., 1899.

excessive hyperæmia of the cortex. This hyperæmia is a recognized cause of epileptic seizures; in fact, as shown by Prus,²⁶ even electrical excitation of the cortex cannot provoke fits after it has been anæsthetized by a local application of cocaine. This is not intended to mean that a high vascular tension due to toxics of internal or external origin will produce epileptic seizures in every one and any one; were it so, the many disorders of the gout series would likewise provoke them. What I do mean is, that in all epileptics *the exciting factor of the seizures themselves*, and irrespective of the condition which renders the subject liable to them, *is a poison formed in the tissues or food residues, toxalbumins*, and that our chief aim, if we are ever to obtain mastery of the dread disease, should be to destroy these poisons and prevent their formation. Is it by saturating the system with bromides—which lower oxidation—that this can be accomplished? Such treatment ignores nature's danger-signals, and gives the spasmogenic poison free sway.

What are the weapons at our disposal that are capable of causing the destruction of these poisons and of preventing their formation?

• Textbooks on the practice of medicine, including the "last editions," continue, regardless of the admonitions of men of large experience to the contrary, to advocate the use of bromides as a *curative* measure. Percy Bryant,²⁷ ten years ago, emphasized the fact that the bromides had added another disease in many epileptics, namely, bromism. Spratling,²⁸ as the result of a close study of several thousand cases at the Craig Colony, concluded that "we must not only regard the bromides as powerless to cure epilepsy," but also "as capable of doing as much harm as they do good as they are ordinarily administered." F. Peterson²⁹ has reported 11 cases in which the number of attacks was greatly reduced by withdrawal or marked reduction of the drug: "in some cases," says this neurologist, "the improvement is startling."

In the light of the evidence I have submitted in the fore-

²⁶ Prus: Wiener klin. Woch., Sept. 22, 1898.

²⁷ Percy Bryant: State Hospital Bulletin, Oct., 1896.

²⁸ Spratling: New York Medical Journal, Aug. 19, 1905.

²⁹ F. Peterson: *Ibid.*, Sept. 25, 1897; and Amer. Med., June 24, 1905.

going pages, the untoward effects of the bromides are readily accounted for. The seizures are due to the presence in the blood of toxic waste products which, by powerfully exciting the vasomotor center, cause an intense rise of vascular tension and violent hyperæmia of the cortex. The logical indication is to prevent the formation of these toxic wastes by measures that enhance the oxidation processes through which they are converted into harmless, readily eliminated end-products. Now, the bromides produce precisely the opposite effect: Wood³⁰ states that "even small doses of bromide are directly depressant to the circulation." Again: "In mammals the bromide acts very much as on frogs, inducing progressive paralysis, depression of temperature, and death by asphyxia when given in small poisonous doses." Asphyxia here clearly points to the drug as one that impairs oxidation, a fact emphasized by the lowered temperature. Chloral, also used considerably in epilepsy, is fully as harmful; Richardson, Hammerstein, and others have found that it could reduce the temperature very greatly—6° C. (10.8° F.), according to the last-named observer.

Of major importance in this connection is the fact that the bromides paralyze a mechanism which, from my viewpoint, is the patient's sheet-anchor, viz., the adrenal system. This action is sufficiently marked in some instances to cause bronzing similar to that observed in Addison's disease. Bourneville and Chapotin,³¹ for instance, refer to Echeverria,³² who witnessed a case in which the brow and neck "were markedly pigmented brown," and to others reported by Voisin; in one of these "the skin of the face was a dark, dirty yellow"; in another it was "covered with bronze patches having no connection with the acne." Inasmuch as it is the adrenal secretion which takes up the oxygen of the air to carry on oxidation (as the albuminous constituent of hæmoglobin) throughout the entire organism, the bromides—chloral as well—inhibit precisely the function which should be activated.

On the whole, it is by preventing the destruction of the toxic wastes which provoke the fits that these drugs are harmful, and it is obvious that their use, under the delusion that they are

³⁰ Wood: "Therapeutics," 13th ed., p. 244, 1906.

³¹ Bourneville and Chapotin: *Le progrès méd.*, Jan. 6, 1900.

³² Echeverria: *Philadelphia Medical Times*, Nov. 23, 30; Dec. 7, 14, 1872.

curative, can only serve to perpetuate the disease unless used, as shown below, with the greatest discretion.

Another very important feature in the treatment of these cases, however, is the diet. In some of my cases this alone sufficed to reduce the number of paroxysms from several a day to one or two a week, and in one instance to cause their cessation as long as the patient abstained from the use of certain foods and beverages, including coffee and tea. The general principle involved in this connection is that we are dealing mainly with poisons formed during the breaking-down of worn-out living substance, *i.e.*, during catabolism, and that these poisons form owing to insufficiency of those constituents of the blood which carry on catabolism and destroy the toxic wastes. In the majority of cases the food-intake is excessive, and the cellular elements are burdened with detritus which cannot be completely converted into eliminable products. The blood, therefore, is loaded with substances which irritate the vasomotor center and thus provoke the seizures.

The practical lesson of this principle is obvious, namely, to allow the patient only the quantity of food strictly necessary to the needs of the body. Indeed, neurologists of wide experience have found that the best results are obtained when the food consists mainly of cereals, milk, fruits, and butter. Some include eggs, but others object to them. Meat, if allowed at all, should be strictly limited to the midday meal, and even then in small quantities. Fats, fried foods, and pastry often prove harmful. Stimulants which tend primarily to cause a rise of the blood-pressure, *i.e.*, alcohol, coffee, and tea, should not be allowed. Gastro-intestinal disorders sometimes suffice to awaken the disease. Appropriate treatment, including daily colon-flushing with normal saline solution, has proven curative in such cases. The patient should also be enjoined to drink water freely, in order to facilitate the elimination of wastes.

As to the medicinal treatment, the indications are remedies which, as I have pointed out elsewhere,³⁴ enhance oxidation, the beneficial effects of thyroid extract in tetany, tetanus, and puerperal eclampsia affording ample proof of their value. Bourne-

³⁴ Sajous: "Internal Secretions and the Principles of Medicine," p. 769, 1903; Monthly Cyclo. of Pract. Med., Jan., 1903; Jour. Amer. Med. Assoc., Feb. 4, 1905.

ville³⁵ found that thyroid extract failed to arrest the seizures, and even increased them. But the cause of this is self-evident: he gave full doses, and thus enhanced general metabolism so actively that he increased the production of wastes. Browning,³⁶ on the other hand, caused the cessation of convulsions in epileptics by giving $\frac{3}{4}$ -grain (0.05 Gm.) doses twice daily. He states that these cases "are due to or associated with disturbances in the general metabolism of the body" and refers to them as "pseudo-epilepsy." All cases of idiopathic epilepsy should be considered in the same light if the term "pseudo-epilepsy" were warranted at all, since, as we have seen, Pierce Clark and others ascribe the disease to "an accumulation of waste-products." Browning's cases were *bona fide* cases of epilepsy, and what they do teach is that small doses of thyroid extract are alone indicated. These, however, as my own observations have shown, must be *very gradually* increased according to the effect on the patient. I usually begin with 1 grain (0.066 Gm.) at each meal, giving a small dose of sodium bromide on retiring at first, if necessary, and gradually reducing the dose until none is given at all. Some cases are benefited by larger doses of thyroid. Thus, in a case treated by a colleague, under my supervision, the nurse, through a misinterpretation of instructions, doubled the dose; the result was considerable improvement. Söchting^{36a} obtained remarkable results also in a case in which hypothyroidia was evident—the underlying cause of cases cured with thyroid.

Osborne³⁷ also refers to a number of cases of epilepsy treated successfully with thyroid, several cases being in women at the time of the menopause and in young girls at the time of puberty. There being no assignable lesions for the epileptic attacks, "I reasoned," says this clinician, "that they must be purely toxic, and that this toxæmia was in excess periodically when the patient should have menstruated. Many of these patients had received bromides, and, while this postponed or controlled the epileptic attacks, general debility and bromism were appearing. In the young girls I used thyroid as an emmenagogue, with the belief that normal menstruation would prevent the attack of epilepsy. I found that it did. I then used the thyroid in the menopause

³⁵ Bourneville: *Le progrès méd.*, vol. xxiv, p. 20, 1896.

³⁶ Browning: *Jour. of Nerv. and Ment. Dis.*, Oct., 1902.

^{36a} Söchting: *Medizin. Klinik*, May 1, 1910.

³⁷ Osborne: *Jour. Amer. Med. Assoc.*, Nov. 3, 1906.

cases, in some continuously in small doses, and in others a few days a month at a possible menstrual epoch. I found that I could control and prevent the epileptic attacks as well with thyroid as could be done with bromides, and with much better results to the system." Similar cases have been reported by A. Gordon,^{37a} Sicard^{37b} found that bromides counteracted actively the effects of thyroid, while Manson^{37c} noted the marked value of thyroid in the epilepsy of cretins—a suggestive relationship.

Briefly, the treatment of epilepsy should have as main object, as I pointed out in 1903,³⁸ *to activate the catabolism of spasmogenic wastes through the adrenal system* and to avoid, as a cure, drugs such as the bromides and chloral, which depress this function. In some instances, the iodides serve a better purpose; the salicylates (or salicin, 5 grains [0.33 Gm.] three times daily) are also effective, as Haig, Vincent,³⁹ and others have shown, but both these agents stimulate the adrenal center and enhance, therefore, the oxidation processes. Such remedies, to keep the blood free of toxic wastes; dietetic measures, to reduce the quantity of such wastes formed; and finally, the free use of water, to insure the rapid elimination with the urine, sweat, etc., of all physiological wastes, constitute a therapeutic triad which soon causes the vasomotor center to lose its irritability, thus preventing the cortical hyperæmia to which the convulsions are due. A small dose of strontium bromide at night, to reduce the hypersensitiveness of the vasomotor center, may be used, but if progress is made without it no bromide had better be given.

Isolated cases in which thyroid proved of value have been reported by a number of observers, who in most instances specify that the bromides had proven ineffectual. A series of 6 cases in which hypothyroidia was discernible were treated by A. Gordon.⁴⁰ In these cases a remarkable change took place, both in the general condition and in the frequency of the epileptic seizures. On the other hand, Pierce Clark⁴¹ used thyroid in 5 cases, which failed to be "attended with very good results." Two

^{37a} Gordon: Penna. Med. Jour., Feb., 1910.

^{37b} Sicard: Jour. de méd. de Paris, Nov. 19, 1910.

^{37c} Manson: Med. Record, Jan. 1, 1910.

³⁸ Sajous: *Ibid.*, p. 769, 1903; Monthly Cyclo., Jan., 1903; Jour. Amer. Med. Assoc., Feb. 4, 1905.

³⁹ Vincent: Journal of Mental Science, April, 1904.

⁴⁰ Gordon: Therapeutic Gazette, Dec., 1907.

⁴¹ Clark: Medical Record, Oct. 24, 1896.

points stand out prominently in these cases: (1) the dose was too large, the initial dose being 5 grains (0.33 Gm.) *t. i. d.*, and (2) cases were selected "in which epilepsy had been a prominent feature in the patient's life since early infancy." Obviously, in the latter instances we were dealing with advanced gliosis, which precluded all hope of cure. Yet, as Pierce Clark says, "all seemed to be benefited for the time being." Even when there is marked gliosis, small doses of thyroid, by preventing the formation of the tidal waves of spasmogenic wastes, will greatly reduce the number of paroxysms if the diet is carefully adjusted to the particular needs of the case. But the best results are obtained, as shown in my own practice, when we have reason to believe that little or no sclerosis is present, and when there is evidence that the underlying cause is hypothyroidia.

OBESITY.—The fact that thyroid preparations in sufficient doses promote the rapid combustion of fats has caused them to be used extensively in this disorder. Given indiscriminately and empirically, in excessive doses, their use has often been attended by distressing after-effects, including asthenia and disorders of vision. When thyroid preparations are employed with due discernment in properly diagnosticated cases, they not only procured marked loss of weight, but also improvement in the patient's general well-being and health.

The cases in which thyroid gland is scientifically indicated are those in which some degree of hypothyroidia exists, and in women in whom panhysterectomy, by removing two organs rich in adrenal rests, the ovaries, has greatly reduced the oxidative power of the blood—a deficiency which affects morbidly the thyroid apparatus as it does all other tissues. In the latter class of cases, therefore, hypothyroidia is also the foundation of the obesity. This may be said also of destructive disorders of the pituitary body which, by depriving the thyroid of its functional impulses, reduce its functional activity. Briefly, in all cases of obesity in which thyroid gland is rationally indicated, the feature to determine is whether directly or indirectly hypothyroidia underlies the adiposis.

In very mild cases, the underlying cause is sometimes difficult to determine; but as a rule, some, very few perhaps, of the typical signs of hypothyroidia may usually be discerned on close



CRETINIC OBESITY.

Case of cretinism aged 21. Effects of four months' thyroid treatment. [Sanderson.]

inquiry. These are chilliness and subnormal temperature, coldness of the extremities and sensitiveness to cold; fatigue on slight exertion; constipation with tendency to tenesmus; more or less frequent attacks of migraine, "sick headaches" with nausea, vomiting, etc., and other periodic manifestations of auto-intoxication—due to inadequate reduction of waste-products and their retention in the blood. The skin taking part in the process of elimination, urticaria and eczema may be found in the history of the case, while transitory oedemas of the brow, around the eyes, and sometimes of the face, even in the absence of albuminuria or casts, may also have occurred. Enuresis is commonly observed in fat, pasty children of this type and may persist to adult age. The patient may be subject to frequent catarrhal disorders of the respiratory passages, usually ascribed to colds, but due mainly to vascular and glandular relaxation. A tendency to early alopecia, including the eyebrows (especially their outer third), is also noticeable in some instances—a sign of deficient general nutrition which coincides with a marked proclivity to early senility. The supraclavicular pads are sometimes discernible when the adiposis is not excessive. Even in the latter case sometimes the pads project beyond the general level.

In women, the menstruation appears late owing to retarded development, and there is a proclivity to metrorrhagia due to laxity of the muscular coats of the uterine arterioles, while pelvic disorders are apt to occur owing to deficient support of the uterus, lack of tone in its muscular elements. Leucorrhœa is also frequent owing to relaxation of the glandular elements of the whole genital tract. Such women conceive readily, but abortion is very frequent among them; if the fœtus is carried to the normal period, they have little or no milk. If the obesity is marked, sterility is the rule; but when such patients are given thyroid gland and their obesity is reduced, they readily become pregnant, as observed by Hertoghe, Montgomery, and others.

Cases of obesity due to hypothyroidia also afford, as a rule, quite a clue as to the presence of this condition, by the statement that none of the dietetic "cures" seemed to improve their condition. Indeed, most of them complain of having been made worse. This is readily explained by the fact that their hypo-

thyroidia could only be aggravated by deficiency of food and forced exercise.

Contraindications to the use of thyroid preparations in obesity have been elaborated by various observers; but perusal of their work indicates clearly that they have been administering excessive doses. Several lives have been lost under these conditions, and many others have been lost by self-drugging. Large doses are always dangerous in the obese, since the heart is itself invariably fatty, while, conversely, small doses are always helpful because they very gradually rid the heart of the fat which compromises its functions and eventually causes death—when the patient has not been carried off by some intercurrent disorders. Even moderate doses have not proven harmful when the patient was under medical surveillance.

The *dose* of desiccated thyroid need not exceed 1 grain (0.066 Gm.) three times daily in any case. This suffices to cause a decrease of weight of from 1 to 3 pounds a week, and sometimes more, Anders⁴² having observed in 2 cases under this dose “a progressive loss of weight at the rate of 4 to 6 pounds per week, respectively, without injury to the general health.” Such doses do not impose upon the patient the need of modifying his usual mode of living and his diet need not, unless excessive, be altered. Occasionally, the dose must be gradually increased to 2 grains (0.13 Gm.) three times daily, but this is seldom necessary.

When the obesity is accompanied by weakness, the appetite is usually increased, especially when, as is my custom, $\frac{1}{50}$ grain (0.0013 Gm.) of strychnine is given with each dose of desiccated thyroid. The patient does best under these conditions, when lean meats, plainly broiled, roasted, or stewed, constitute the increase of his dietary. This treatment is valuable in another direction: it tends to counteract any tendency to constipation that may be present.

The *untoward effects* most frequently met with in obese subjects are of cardiac origin: marked discomfort in the precordia; dyspnoea, with tendency to heart-failure. In some instances this has been followed by death, when marked fatty degeneration happened to be present. But, as stated, these do not

⁴² Anders: “Practice,” 8th ed., p. 1276.

occur when small doses—1 grain (0.066 Gm.) of the desiccated thyroid—are used. Even the greatest watchfulness will not prevent toxic effects when large doses are administered, since the accumulation of the thyroid principle proceeds at a rapid rate and the milder symptoms of thyroidism are almost at once followed by its acute manifestations—those previously described.

Adiposis Dolorosa; Dercum's Disease.—Having had no personal experience in the treatment of this rare disease, the following quotation from a comprehensive article by Professor Dercum, soon to appear, is presented:—

“In the treatment of *adiposis dolorosa* one remedy has in a few cases proved of value, and that is thyroid substance. This should be given in doses of from $2\frac{1}{2}$ to 5 grains (0.165 to 0.33 Gm.) three times daily, for a very long time. The salicylates, notably aspirin, are of decided value in relieving the pain. The best plan of procedure, as a matter of course, is to place the patient in bed, and to institute a systematic course of treatment. The rest should be absolute and should extend over several months of time.

“The patient should be weighed when treatment is begun and thyroid substance given at first in small and then in somewhat larger doses. At the same time a diet should be instituted that is largely free from carbohydrates and fats. It should be remembered, however, that a diet, no matter how rigid, will of itself make no impression in *adiposis dolorosa*; it will fail absolutely. It is, of course, wise to institute a careful diet, but patients do better when the diet is not too strict. Inasmuch as the affection is attended by a marked asthenia, the diet should be nutritious. It should consist of the red meats in moderation, the white meats freely, the succulent vegetables, eggs, and skimmed milk. The latter can be used between meals, and, if necessary, also at mealtimes.

“The pains are not infrequently controlled or, at least, made better by aspirin or salophen in full doses, 10 or 15 grains (0.66 or 1.0 Gm.) three times daily after meals. Sometimes the tenderness and soreness are better borne when the limb or part affected is gently supported by a flannel roller; if the tenderness be extreme a layer of cotton-wool may first be applied.

"Just as soon as the tenderness permits, gentle massage should be instituted; sometimes this can never be employed; in other cases, again, it can be instituted comparatively early, and there can be no doubt that in a measure it favors the diminution of the swellings, especially if the patient can bear deep kneading. Bathing between blankets, as in ordinary rest treatment, should also be carried out, but of themselves baths accomplish nothing in *adiposis dolorosa*; indeed, the physical exertion and manipulation attendant upon the application of ordinary hydrotherapeutic measures in these cases exhausts the patient.

"It is a good plan to keep a record of the pulse and temperature during thyroid administration, although the writer has never observed any fluctuations of moment in these cases, even when the thyroid was pushed. The patient should, of course, be weighed from time to time, and the dose of thyroid modified according to the impression made. In some cases no impression whatever can be made; in other cases, again, the impression is decided. In 3 cases of the writer the result was most satisfactory; 2 of these were treated systematically by rest in bed; the third could not, for certain reasons, be put to bed. In all 3 the improvement in the size of the swellings and in the lessening of pain was very great. Treatment was carried out six months to a year. In 1 case the affection recurred at the end of two years, but was again controlled. In the second, improvement and practically good health has persisted for four years. The third was greatly improved, and has disappeared from observation."

GOITER.—As Rogers⁴³ states: "Simple goiter, or hypertrophy of the thyroid gland, is usually considered to be a disorder which is entirely distinct from Graves's disease, and to represent a totally different pathological process; but there are many reasons for doubting this conclusion and for suggesting something of the same pathological physiology, at least, in the origin of both exophthalmic goiter and simple goiter." Yet we are confronted with the fact that thyroid preparations are often useful in goiter, whereas in the active or erethic stage of exophthalmic goiter it is harmful. This is explained,

⁴³ Rogers: *Annals of Surgery*, Dec., 1909.

from my viewpoint, however, by the fact that we are dealing in goiter with a compensative reaction very similar to that which occurs in cases of exophthalmic goiter, as previously stated. The presence of some toxic in the blood (goiters are now generally ascribed to the presence of some unknown toxic in the drinking water of the regions in which they occur endemically) creating a demand for an increase of thyroiodase as one of the antitoxic constituents of the blood, the organ is unable to furnish it. Being subjected to undue stimulation, the local expression of which is excessive vasodilation, it becomes enlarged, *i.e.*, goitrous. Briefly, in those cases in which thyroid preparations are effective, the goiter is the result of a toxæmia which the added thyroid substance helps to counteract as one of the physiological antitoxic agents.

In some of these cases, however, both iodine and thyroid gland seem to produce pernicious effects. Even minute doses, as observed in one of my cases, suffice sometimes to produce distressing symptoms. It is always advisable to begin with fractions of doses and to increase gradually until the beneficial dose. Beginning with $\frac{1}{2}$ grain (0.033 Gm.) three times a day, the dose can be raised gradually to 2 grains (0.13 Gm.), but in most cases 1 grain (0.066 Gm.) suffices to compensate for the inability of the organ to supply the volume of thyro-parathyroid secretion required by the organism at large.

The dietetic and other measures indicated in these cases are those recommended for exophthalmic goiter, to which the reader is referred (page 229, this volume). The great value of surgical intervention is not to be overlooked, however. In competent hands the post-operative mortality has been practically reduced to *nil*, and when we consider that a simple goiter may assume the more formidable type of exophthalmic goiter our duty is to afford the patient this, the surest, guarantee against it when medical treatment, including the use of thyroid, fails to turn the tide toward recovery.

CHRONIC RHEUMATISM.—In the treatment of this disease we owe much to the patient labors of Léopold-Lévi and H. de Rothschild.⁴⁴

⁴⁴ Léopold-Lévi and Henri de Rothschild: "Étude sur la physio-pathologie du Corps Thyroïde et de l'Hypophyse," 1908; "Nouvelles études sur la physio-pathologie du Corps Thyroïde et des autres Glandes Endocrines," 1911.

These leave no room for doubt that thyroid gland is of great value. In a series of 39 cases ranging from the ages of 12 to 75 years, 32 were greatly improved, cure being obtained in 2 severe cases. All the concomitant symptoms, such as œdema, neuralgia, etc., were favorably influenced; it increased the appetite, caused the cardiac anginas and all neural phenomena to disappear.

Two examples of the results obtained will serve to illustrate both the treatment resorted to and the doses employed. Both were cases of chronic rheumatism with hydrarthrosis. In one of these the hydrarthrosis followed a fall from a bicycle, and was the precursor of attacks of muscular rheumatism, all the joints being gradually involved in the morbid process. Notwithstanding seasons at Aix-les-Bains, Dax, and other stations, the patient became quite impotent, having even to be fed. The usual remedies proved unavailing, though aspirin and iodine seemed, at least for a while, to be of some benefit. The patient's condition becoming steadily worse, thyroid extract was tried, beginning with $1\frac{1}{2}$ grains (0.1 Gm.) every other day during ten days, followed, after five days, by resumption of the remedy; then giving again only $1\frac{1}{2}$ grains (0.1 Gm.) every other day. This dose was gradually increased until, eleven months later, the patient was taking $7\frac{1}{2}$ grains (0.5 Gm.), in divided doses, daily. Good results have also been recorded by Revilliod, Lancereaux, and others.

The interpretation of the pathogenesis of rheumatism I submit elsewhere in this work affords an explanation of the manner in which these results are obtained. Briefly, from my point of view, rheumatism is due to the presence in the blood of any toxin, or toxic, especially toxic wastes derived from excessive tissue metabolism, capable of exciting violently the adreno-thyroid center, and of increasing to an abnormal degree, therefore, the functional activity of the adrenal system. The proportion of adrenoxidase in the blood being very greatly increased, as shown by the tendency to hyperthermia and the anæmia (due to hæmolysis), there occur (1) hyperconstriction of all vessels owing to excessive metabolism in their muscular coats, and, as a result, hyperæmia of all capillaries (which are not provided with such a coat), including those of

the serous membranes, especially those of the joints, and also, (2) as a result of hyperoxygenation of the pancreas and leucocytogenic tissues and hyperstimulation of the thyroid apparatus, an accumulation of autotoxic bodies in the blood-plasma, and effusion into the joints, serous membranes, glandular elements, etc. Hence the swelling, heat, severe pain, accumulation of fluid, and the inflammatory lesions, including erosion in the joints; hence also the marked predilection of serous membranes, the pericardium and endocardium, the myocardium, the tonsils, etc., to inflammation; hence, finally, the fibrous adhesions in the joints and around the neighboring structures which provoke ankylosis.

While the toxins of various bacteria, the staphylococcus citreus, the micrococcus lanceolatus, the gonococcus, may stimulate the test-organ sufficiently—especially in individuals in whom this organ is hypersensitive—to provoke acute rheumatism, it is caused in most cases by intermediate toxic waste-products which appear in the blood as a result of exposure to cold and the resulting hypocatabolism—the cellular trypsin failing, when the local temperature is below normal, to break down adequately wornout cell material.

Chronic rheumatism differs from the foregoing, in that the cause of the disease is inadequate catabolism of tissue wastes and excitation, by the toxic products formed, of the vasomotor center, while the pathogenesis of the joint lesions includes more or less increase of the vascular tension, as in the acute form.

Under these conditions, it is obvious that thyroid gland, by increasing the proteolytic activity of the blood, promotes destruction of the toxic wastes which underlie the disease.

Analyzing Lévi and de Rothschild's results from this viewpoint, the manner in which they were produced by their *small doses* becomes self-evident. Thus, increase of appetite was the first effect noted; this is a normal result, since the greater cellular activity and catabolism created a greater demand for foodstuffs. Increased heat production soon replaced the marked and constant chilliness from which the patient suffered—an effect due to the marked increase of oxidation the thyroid extract engendered throughout the body. The dose

was increased to $1\frac{1}{2}$ grains (0.1 Gm.) one day, then to 3 grains (0.2 Gm.) the next, this being continued ten days. After a period of rest of five days, 3 grains (0.2 Gm.) were again given daily. The pain became less—a fact due to decrease of the vascular tension, owing to increased destruction of the toxic wastes which excite the vasomotor center, thus causing constriction of all arteries. The sensory nerve-terminals being relieved of the hyperæmia which caused the pain, the latter became less marked in proportion. Closely connected with this beneficial action was the effect on the joints, viz.: the *hydrarthrosis became reduced*. Being also due to excessive vascular tension, it is plain that, by causing vasodilation in the manner just explained, thyroid extract caused the excess of fluid to leave the joints. The dose being still further increased until $7\frac{1}{2}$ grains (0.5 Gm.) were taken daily, *emaciation* occurred—a well-known effect due to excessive catabolism provoked by large doses of thyroid extract.

Eleven months' treatment brought Léopold-Lévi and Rothschild's case back to a condition of comfort, the joints having resumed their shape and flexibility—with the exception of one knee, which remained ankylosed—owing doubtless to fibrosis, a condition beyond the reach of the remedy. This does not militate against its use, however; it simply shows that the treatment was resorted to too late to avoid irremediable organic lesions. Rheumatism with eczema and epilepsy in the child also disappeared under thyroid treatment in a case of Léopold-Lévi's.^{44a}

In a case treated by Parhon and Papinian⁴⁵ thyroid extract produced, though the disease was of twenty-four years' standing, "a true regeneration." When $7\frac{1}{2}$ grains (0.5 Gm.) in five divided doses daily had been given some time, palpitations, tachycardia, and arrhythmia appeared. On withdrawing the remedy these untoward effects ceased, but recurred as soon as its use was resumed. This affords additional evidence in support of a fact I have often urged, viz.: that the best effects of thyroid extract are obtained with *small* doses.

These results have been confirmed by other observers,

^{44a} Léopold-Lévi: Soc. de Méd. Paris, Oct. 28, 1911.

⁴⁵ Parhon and Papinian: Presse méd., No. 1, p. 3, 1905.

notably by Combe, F. Claisse,⁴⁶ Souques,⁴⁷ Ménard,⁴⁸ Claisse and Vincent,⁴⁹ and more recently by Steele-Perkins^{49a} and Wilson.^{49b} Though thyroid products act very gradually, and require patience and careful watching, the method is a very promising one.

ENURESIS.—In many instances this condition is due to general asthenia, and the muscular debility which attends this state carries along with it inability of the sphincters to perform their functions at all times, especially when, during sleep, general relaxation prevails. The influence of thyroid on general metabolism and nutrition and the resulting increase of functional power in all organs affect equally both the cystic and urethral sphincters and thus overcome the trouble.

According to Hertoghe,⁵⁰ nocturnal incontinence of urine in young children and adolescents is due to thyroid insufficiency. He observed a number of cases in which the use of thyroid extract was followed by improvement or cure. Children who suffer from incontinence are often undersized, and they present the infantile habitus in varying degrees—improperly placed teeth, nasopharyngeal adenoids, flat chests, and emaciated and slender extremities. Such patients—those in which thyroid gland will prove beneficial—are often flat-footed and their feet have an offensive odor, their gait is stiff, they suffer from pains in the thighs and from sciatica produced by the cold and moist surroundings in which they lie at night. The systematic examination of the urine in these cases shows an abundant deposition of the cells covering the free surface of the cystic mucosa. In children beyond 2 years of age Hertoghe gives 2 grains (0.13 Gm.) daily with 3 to 5 grains (0.2 to 0.33 Gm.) of potassium iodide and the bromides on retiring.

Additional signs are subnormal temperature, deficiency of hair in the external third of the eyebrows, as observed by Léopold-Lévi and de Rothschild; scaphoid scapulæ, delayed epiphysial development, as determined by the X-rays, and adenoid vegetations. In such cases removal of the latter fails to benefit the patient. Thus, Leonard Williams⁵¹ reported a case

⁴⁶ Claisse: *Klinisch-therapeutische Woch.*, S. 979, 1899.

⁴⁷ Souques: *Ibid.*, p. 1003, 1908.

⁴⁸ Ménard: *Tribune médicale*, No. 9, 1908; *Rev. intern. méd.*, p. 326, 1908.

⁴⁹ Claisse and Vincent: *Münch. med. Woch.*, S. 1667, 1908.

^{49a} Steele-Perkins: *London Lancet*, March 5, 1910.

^{49b} Wilson: *British Medical Journal*, Dec. 10, 1910.

⁵⁰ Hertoghe: *Bull. de l'Acad. Roy. de Méd. de Belgique*, vol. xxi, No. 4, 1907.

⁵¹ Williams: *London Lancet*, May 1, 1909.

of enuresis in a 9-year-old boy in which he tried removal of the adenoids. The operation made the boy much worse, however, and, believing that the removal of the adenoids deprived the boy of a necessary internal secretion, he then gave him thyroid extract, $\frac{1}{2}$ grain (0.033 Gm.) twice daily. The result was instantaneous and complete, the boy no further wetting the bed. Twenty-four other cases were thus treated. Only one of these proved rebellious to the treatment. The essential point to remember is that thyroid gland is useful mainly in cases in which there exists hypothyroidia, some sign of which can always be discerned if it is at all present. Firth obtained marked improvement in 16 out of 28 cases with small doses, especially when the enuresis had persisted since birth.

SKIN DISEASES.—A prolonged trial of thyroid preparation in many diseases of the skin has led dermatologists to the conclusion that they were indicated in disorders due to deficient metabolism. As stated by Winfield, these include the erythematobulbous type, which includes *dermatitis herpetiformis*, and the psoro-eczematous type, to which belong *prurigo*, *psoriasis*, and *chronic eczema*.

This is explained by the action of thyroid products on oxidation and metabolism, as is well shown in the effects noted by Don: 1. Increased nutrition of the skin; hence its probable remedial action in ichthyotic conditions: an effect produced without any necessary abnormal perspiration. 2. Increased action of the cutaneous glands, accelerating excretion of waste-products, thus keeping the surface in a supple condition. 3. Regrowth of hair, as shown in myxœdema and some cases of general alopecia. 4. Increased activity of the epidermal layers, causing desquamation of unhealthy epidermis and reproduction of a new covering, as observed in ichthyosis, psoriasis, dry chronic eczema, and at times in myxœdema and cretinism.

Eason⁵² reported several consecutive cases of *eczema in young children* successfully treated by thyroid. In the first case, 14 months old, the baby had suffered from eczema of the face for nearly a year. This had been entirely resistant to the usual applications and internal treatment; nor was hospital

⁵² Eason: Scottish Med. and Surg. Jour., May, 1908.

^{52a} Firth: London Lancet, Dec. 2, 1911.

treatment more efficacious. Two and a half grains (0.165 Gm.) of a thyroid tablet was given daily. In a little more than one month the child was entirely well. His cure persisted for nearly a month, when the disease showed a tendency to recur. The second course of thyroid was followed by a permanent cure. The 4 other cases gave similar results. Moussous⁵³ observed 2 cases of eczematous seborrhœa successfully treated with thyroid. In the first case the scalp was normal at the end of two weeks; in the second in one month. Complete cure occurred in both cases, and has persisted.

In *psoriasis* thyroid is harmful when the eruption is developing, but it sometimes acts with surprising efficacy in fully developed cases. The untoward effects observed by dermatologists, however, are in great part due to the fact that they use too large doses. These, as previously stated, enhance metabolism violently and increase the waste-products in the blood and therefore the cutaneous disorder.

Pedrazzini⁵⁴ observed 5 cases of *scleroderma*, in 4 of which the thyroid was small and atrophied, while in the other the thyroid was large and hard. Thyroid treatment gave good results in the two in which it was applied, commencing with small and progressive doses. None of the patients presented signs of nervous changes suggesting atrophic origin, but everything confirmed the assumption of some connection between the cutaneous affection and the thyroid gland.

Thyroid has been tried in *lupus* by a number of observers. Though the results were contradictory, the bulk of the evidence indicates that it is worthy of more extensive trial. Owing to its influence on oxidation it enhances the nutrition of the skin and thus antagonizes the destructive process while promoting that of repair. As full doses have to be used during a prolonged period, the patient should be carefully watched. Thyroid has been tried in *leprosy*, but the results were not encouraging, though the remedy was pushed as far as safety would allow.

In a case of *hypertrophic rosacea* which has resisted all forms of treatment, Isadore Dyer, of New Orleans, used thyroid with, for local use, a salve containing resorcin 3j; rose water

⁵³ Moussous: *Archives de méd. des enfants*, Mar., 1908.

⁵⁴ Pedrazzini: *Gaz. degli Ospedali*, Aug. 1, 1909.

5iv; lanolin ad 3vj. After two months there was decided improvement, the skin being soft and normal to the touch and the color greatly improved. The patient was discharged cured after three months of thyroid medication.

HÆMOPHILIA.—The various preparations of thyroid gland are extremely valuable in this dyscrasia, due to a deficiency of fibrin ferment in the blood. As this body, according to my researches, is mainly composed of the adrenal product, the increased functional activity of the adrenals, provoked by thyroid preparations administered, increases the blood's asset. The coagulation time in hæmophilia may be brought down from over ten minutes to three or four minutes in adults by 2-grain doses of the desiccated thyroid three times daily after meals. This is equally effective when operations become necessary.

Examples of the value of thyroid gland in a large proportion of cases of hæmophilia (we might say all, for the cases of recurrent hæmorrhage in which it fails are doubtless due to other causes) are now numerous in literature. Combemale,⁵⁵ for instance, cites the case of a woman who, for the preceding two years, had been suffering from hæmorrhages from the larynx. She was covered with purpuric spots, her gums bleeding. She was extremely weak and exhausted. Treatment with thyroid tablets was commenced; in ten days very marked and evident improvement; there was no purpura, no bleeding from the gums. In ten more days she had perfectly normal menses; all other hæmorrhages stopped. Scheffler⁵⁶ reported a case in which hæmophilic epistaxis was absolutely unaffected by ordinary therapeutic agents, and the epistaxis became so persistent and exhausting that permanent blocking of the nasal fossa was necessary. Treatment by thyroid extract exerted an immediate and beneficial effect, and was followed by cure. In three days the violent and persistent epistaxis had practically stopped. In six days, about 8 grains (0.53 Gm.) of thyroid gland having been given daily, the purpuric eruption ceased. A marked case in which the patient had become extremely anæmic was also reported as recovered by Rugh,⁵⁷ under the use of 5-grain (0.33 Gm.) doses three times daily.

⁵⁵ Combemale: *La médecine moderne*, April 30, 1898.

⁵⁶ Scheffler: *Archives de méd. et de pharm. militaire*, March, 1901.

⁵⁷ Rugh: *Annals of Surgery*, May, 1907.

The value of thyroid in the preparation of hæmophilic cases for serious operations is well illustrated by W. J. Taylor²⁸ in 3 cases. The coagulation time was reduced with 3-grain (0.2 Gm.) doses three times daily from twelve minutes to three minutes, and the operations, including a nephrectomy, proved drier if anything than if they had been performed in a non-hæmophilic subject. The desiccated thyroid on the market, especially the standardized product, being stronger than that available in former years, 2 grains (0.12 Gm.) three times daily need not be exceeded even in these cases.

SURGICAL DISORDERS.—We have seen that in 1907 I pointed out that the thyroparathyroid secretion corresponded with what Sir A. E. Wright has termed opsonin. During the same year I urged that thyroid preparations, owing to their influence on oxidation and their power to increase both the opsonins and the germicidal activity of the blood, were indicated in the *early stage of tuberculosis*—mainly on account of the content of the tubercle bacillus in phosphorus, viz.: 55.23 per cent. of its ashes—a fact sustained clinically. Recently, Frugoni found not only that thyroid gland markedly raised the opsonic index of tuberculous animals, but also the active germicidal power of their blood. That this should entail in the surgical field marked progress in the treatment of all conditions due to tuberculosis is self-evident. In *hip-joint disease* and other *tubercular bone processes*, for example, thyroid is clearly indicated.

Besides its powerful stimulating action on the defensive functions, thyroid gland, as shown by Parhon, Macallum, and others, hastens calcium metabolism. This accounts for its value in *osteomyelitis* and *rhachitis*. We have striking evidence of its efficiency in the treatment of deficient metabolic activity in osseous tissue in the rapid growth of the skeleton in cretinism brought about with its aid. This has suggested its use in *delayed union in fractures*—where it is valuable only when more or less hypothyroidia exists—and accounts for its greater value for this purpose in the young than in the adult, its therapeutic action in this class of cases growing less as age advances.

Another indication for thyroid preparations, owing, however, mainly to their influence on general oxidation and metabo-

²⁸ Taylor: *Monthly Cyclopædia*, July, 1905.

lism, is in *hypothyroidia in operated subjects*. The presence of this condition, a larval and covert form of myxœdema indicated mainly by a tendency to obesity, cold hands and feet, dry skin, brittle hair perhaps, mental and physical torpor, rheumatic pains in the occiput and back usually treated unavailingly for rheumatism. Here deficient oxidation and metabolism entail a correspondingly deficient production of opsonin and other protective bodies. Such cases are readily infected, and their recovery after any operation, even sometimes after a trivial one, is unusually slow. A preparatory course of thyroid gland transforms completely such a case into one in which the chances of a successful result are as good as in a normal individual.

In *febrile infections* the thyroid gland is sometimes so active that it becomes enlarged and even quite painful. This is now recognized as a distinct effort to raise the protective process to adequate efficiency. In surgical diseases such as *septicæmia* and *erysipelas*, aid afforded to the gland by administering thyroid preparations has been found to curtail these diseases. It fulfills in a measure the rôle of antistreptococcic serum. This applies also to *suppurative processes* of all sorts due to general adynamia; the rapidity with which it produces beneficial effects in this class of disorders is sometimes striking. This applies also to suppurative processes situated in special organs, such as eye, ear, nose and throat, and the sinuses.

When the purpose is to increase the germicidal and anti-toxic power of the blood, and also phagocytic activity, in any of the foregoing disorders, excepting pulmonary tuberculosis, the dose required must be somewhat larger, but not excessive. A condition similar to Wright's negative phase in vaccine therapy is readily brought about by excessive doses. In the laboratory such doses decrease instead of increasing the resistance of animals to infection. Again, as personal investigations have suggested, there is good ground for the belief that the so-called untoward effects observed under thyroid medication are closely allied to anaphylaxis. Two grains of the desiccated gland in tablet form slowly increased to 3 grains, three times a day, is the maximum that should be administered in the adult, and the patient should be carefully watched to forestall any undue

action of the remedy. The best indication of any untoward effect, we have seen, is the pulse. Any considerable quickening or palpitation indicates that the remedy should be discontinued a few days, then resumed in smaller doses. Again, the preparations on the market vary in strength. The above dose refers to Armour's or Burroughs, Wellcome & Co.'s desiccated gland, which is standardized two-tenths of 1 per cent. of organic iodine.

In *cancer*, as will be shown in the second volume (see page 1389), thyroid gland is valuable in inoperable cases and after extirpation to prevent recurrence. As I emphasized in 1907, however, its best effects in the treatment of the disease are obtained when X-rays or radium and saline solution are employed concomitantly.

PARATHYROID ORGANOTHERAPY.

The physiology of the parathyroids was reviewed in the third chapter. We saw therein that the prevailing view was, that their secretion served to neutralize the toxic wastes which give rise to tetany, and that it influenced calcium metabolism. I defended therein Gley's opinion, that it supplemented the function of the thyroid gland, and, moreover, my own previously advanced conclusion, that thus combined the thyro-parathyroid secretion increased the germicidal and antitoxic power of the blood by endowing the albuminous portion of the haemoglobin with sensitizing properties, and that, as such, it was the blood constituent Sir A. E. Wright had termed "opsonin." Just what rôle the parathyroids fill in the dual process cannot at present be determined, but the fact that, as shown by Gley, the proportion of iodine in them is much greater than in the thyroid proper suggests that it supplies the most active component of the compound secretion, that part of it which has to do with the sensitizing or opsonic action. This is due, we have seen, to the iodine itself, owing to the peculiar property it possesses of increasing the inflammability of phosphorus.

From the standpoint of organotherapy, it is this property that we must bear in mind. We must look upon parathyroid glandules or adequate preparations of these organs as the essence, so to say, of the whole thyroid apparatus, in so far

as its antitoxic properties and its rôle in calcium metabolism are concerned. This agrees with the teachings of experimental evidence, particularly that afforded by Jeandelize,⁵⁹ which have shown that the secretory product of the thyroid gland proper is more concerned with the processes of general nutrition and development than with the auto-protective function.

The manner in which the parathyroids affect the organism and the influence of parathyroid gland as a remedy seem to me best illustrated in the symptomatology and treatment of the first condition analyzed on the opposite page (741) under the title of "hypoparathyroid tetany."

As to the preparations available, Berkeley⁶⁰ claims that the only available glands are those from the bullock, and these are hard to find anatomically—as I know from experience—and expensive. He no longer uses the preparations obtainable on the market, and employs only glands obtained fresh at the abattoirs under his own supervision. He found that the gland could be administered either as fresh gland, preserved gland or nucleoproteid solution. In the author's words:—

"The *fresh gland* is given in the simplest manner possible, minced and eaten in a bread-and-butter sandwich. The dose is from 5 to 8 glands per day. This method is, of course, available only for patients living near a large abattoir where someone has been taught how to find the material.

"In the matter of *preserving the gland*, the essential thing is to get the tissue finely divided and in intimate contact with the preservative. The glands are trimmed with sterile instruments, dried between folds of sterile gauze, and rubbed up patiently in a mortar with an excess of milk-sugar and a small percentage of boric acid to a fine, dry powder. A trace of oil of peppermint is usually added. Prepared in this way, dispensed in capsules, and kept on ice, they keep from four to six weeks. The dose is 5 to 8 per day, each capsule corresponding to $\frac{1}{2}$ a grain [0.033 Gm.] of fresh gland. They are now for sale in several New York pharmacies.

"The *nucleoproteid* (S. B. Beebe's method) is extracted as follows: The glands are thoroughly triturated—a few at a

⁵⁹ Jeandelize: "Insuffisance Thyroïdienne et Parathyroïdienne," Nancy, 1903.

⁶⁰ Berkeley: Old Dominion Journal, April, 1909.

time—in a mortar with laboratory sand. The triturate is made distinctly alkaline with lithium carbonate solution and extracted with normal salt solution in excess. The process of extraction takes twenty-four hours. The container is frequently shaken, and between whiles placed on ice. The solution is now filtered, and finally acidulated with a few drops of 10 per cent. acetic acid. The nucleoproteid settles to the bottom as a voluminous, flocculent, white precipitate. In two hours the overlying fluid, which is now clear, and contains no albumin at all, and only a little globulin, is decanted, and the precipitate is redissolved by adding a little more lithium carbonate, till a slight alkaline reaction is again obtained. This concentrated solution may be diluted to any desired strength. I usually dilute till the number of c.c. is equal to the original number of fresh glands used. The dose of the preparation is about 20 drops [1.23 c.c.] per day. It is readily preserved with a little chloroform or thyroid, and if kept on ice stays effective about half as long as glycerinated vaccine virus, or diphtheria antitoxin. To make it suitable for hypodermic use, it should be more concentrated than as described above, carefully standardized, run through a Chamberland filter, and put up in sealed tubes."

Proceeding with the consideration of the few disorders in which parathyroid has been used, it was deemed best to treat the first of these, hypoparathyroid tetany, in the same manner as other diseases of the ductless glands reviewed in the earlier chapters of this volume, owing to the important position this disorder now occupies in the clinical, and to the fact that it is scantily, if at all, treated in works on surgery.

HYPOPARATHYROID TETANY. (Tetania parathyreopriva; Parathyroid Tetany; Hypoparathyrosis; Cachexia Parathyreopriva; Status Parathyreoprivus or Hypoparathyreoprivus.)

Tetany due to hypoparathyroidia occurs as a result of any condition which temporarily or permanently arrests the functions of the parathyroid glandules. The form most generally recognized at the present time is that variously known as tetania parathyreopriva, cachexia parathyreopriva, status parathyreoprivus, which follows removal of the parathyroids along with the thyroid in goiter and other growths of this gland—a subject

already treated on page 174. The second form is due to organic lesions, such as tuberculosis, interstitial hæmorrhages, inflammatory lesions during infections, etc., of the parathyroids sufficient to greatly impair their secretory activity. These organs being the source, with the thyroid, of one of the auto-defensive constituents of the blood, as previously shown, their functional arrest allows those poisons—toxic waste-products in the present connection—to accumulate in the blood and to provoke tetany and even, in very severe cases, the clonic convulsions of epilepsy.⁶¹ In its general terms, therefore, hypoparathyroid tetany may be defined as follows:—

Hypoparathyroid tetany is a disorder due to impairment or arrest of the secretory activity of the parathyroids, characterized by more or less severe spasms or convulsions, the result in turn of accumulation in the blood of toxic waste-products, which it is one of the functions of the parathyroid secretion, as the opsonic constituent of thyroiodase, and along with other antitoxic constituents of the blood, to convert into benign, eliminable end-products.

SYMPTOMATOLOGY. *Post-operative Parathyroid Tetany.*—The symptomatology of this disorder may vary considerably in intensity and in the time and manner in which it appears. In most cases, however, the tetany begins by a sensation of stiffness around the mouth with twitching of the facial muscles and tingling or formication. This is soon followed by stiffening of the masseter muscles and fibrillary contractions or rigidity of the tongue—which causes difficulty of speech and deglutition—and finally locking of the jaws, as in true tetanus. This is often accompanied by trembling of the eyelids. The thumbs and then the hands are thrown backward, *i.e.*, in marked extension, the fingers assuming either the claw-like or “*main en griffe*” shape, or, with two fingers, the index and medius, extended, the “obstetric position.” There is at the same time flexure of the forearms, often complicated with more or less severe pains in the flexed muscles. The feet are also cramped, often in the equinovarus position, the pain being then located in the calves. In severe cases opisthotonos may occur, the body being supported only on the head, shoulders, buttocks, and

⁶¹ See pp. 1429 and 1437, vol. II, for the pathogenesis of tetany and tetanus.

heels. There is a feeling of intense tightness around the heart. The respiratory muscles, thoracic and pulmonary, being likewise contracted spasmodically, respiration becomes difficult, sufficiently so at times to provoke intense dyspnoea and cyanosis. There may also be marked strabismus, dilatation of the pupils, frothing at the mouth, and clonic movements similar to those observed in true epilepsy.

The pulse becomes rapid and weak and sometimes irregular during the attacks, and the temperature is raised. As explained in the article on tetany in the second volume, the latter symptom is partly due to the presence of an excess of adrenoxidase in the blood and the increased oxidation this entails—the adrenal center being stimulated by the toxic wastes accumulated in the blood—and partly to the rise of blood-pressure, which causes blood to be driven from the deeper vessels to the periphery, and then to congest the cutaneous capillaries. When marked this phenomenon also causes burning sensation over the entire body.

Tetany may occur almost any time after the operation, the period of onset varying greatly. As a rule, however, the first signs occur the third or fourth day after the operation, the intervening period representing doubtless that during which the supply of thyroiodase is being exhausted. The frequency of the paroxysms also varies in different cases, from one to many a day, according in a measure to the diet and amount of exercise to which the patient is subjected. In some cases the parathyroids are only injured during the operation, and their recovery ends the tetany.

Non-operative Hypoparathyroid Tetany.—The symptoms of this condition do not vary from those just described, though they are less marked. In some cases, in fact, they hardly exceed in intensity those produced by strychnine in full therapeutic doses, when the physiological limit of the drug has been reached. Here the parathyroids are able to carry on their functions only in part, the lesions produced in them by local disease, tuberculosis, interstitial hæmorrhage, etc., having left perhaps one or more of the organs or a part of their parenchyma intact. The thyroiodase formed under these circumstances being deficient in the constituent which endows it with its anti-toxic properties, it allows the spasmogenic poisons to accumulate

in the blood very gradually, and in relatively small quantity as compared to that which invades the blood when all the parathyroids are destroyed by operation or disease.

In these mild cases, the identity of the disorder present may be determined by various signs: Trousseau's, tapping or pressure upon large nerve-trunks to elicit muscular contractions; Chvostek's, the production of spasm of the facial muscles by tapping over the facial nerve close to the parotid or over the muscle itself; Hoffmann's, the percussion of sensory nerves to demonstrate hyperæsthesia; Erb's, hyperæsthesia of the nerves under electric stimulation. All these phenomena are explained by the fact that, as previously urged (see also the articles on Tetany, page 1429, and Tetanus, page 1437, in the second volume), the spasmogenic toxic excites the vaso-motor center, producing thereby contraction of all vessels and driving the blood from the great deeper channels to the periphery. All peripheral muscles and nerves being rendered hyperæmic, they become correspondingly sensitive to irritation and stimulation.

Careful differential diagnosis is necessary in these cases, since tetany is also produced, irrespective of any parathyroid disorder (though the parathyroids may show active hyperplasia, as observed by MacCallum, in a fatal case of gastric dilatation), by many other disorders: gastric and intestinal, pregnancy and lactation, uræmia, violent excitement and exertion, etc.—all conditions in which the blood becomes laden with toxic substances. Infectious diseases are also prominent causes of tetany, but probably in part through the lesions of the parathyroids they sometimes produce.

TREATMENT.—Tetany should always be borne in mind when any operative measure involving the thyroid is to be resorted to, since post-operative tetany would never occur if the parathyroids were always spared. Referring the reader to works on surgery for details, it may be mentioned here that every effort should be made to protect not only the parathyroids themselves by preserving the posterior capsule of the thyroid, upon which they lie, but also to so ligate the thyroid vessels with which they are connected as to provide for uninterrupted circulation through them. I would suggest also that their lymphatic connections be as much as possible spared, since, as we have seen, the

parathyroid product reaches the venous circulation through their intermediary.

Important in this connection also is the selection of the portion of the thyroid that is to be removed. Kocher, according to Erdheim,⁶² who generally removes the central part of the gland, has "hardly ever had a loss from cachexia strumipriva or tetany." Again, complete removal of the thyroid itself is never justified, and as large a portion of the organ as possible should be left to insure the continuation of the function it fulfills in conjunction with the parathyroids. If the parathyroids are accidentally removed with the thyroid, which a careful examination of the extirpated organ should enable the surgeon to determine, they should at once be dissected out and implanted into the cervical tissues, selecting as much as possible a region rich in blood-vessels.

In some cases, operated with due care, the parathyroids left *in situ* may be injured, or suffer, perhaps, from shock. Under these conditions, mild tetanic symptoms may occur temporarily. In 500 thyroidectomies performed by von Eiselsberg⁶³ in about seven years, 15 showed Chvostek's sign, but it disappeared without treatment in a few days. In 10 cases there was well-developed tetany, with one death, total removal of the parathyroids in the latter being probable.

W. H. Brown⁶⁴ rightly criticises the indifferent attitude of some surgeons concerning the importance of the parathyroids to the organism, and sustains his position by an extremely severe case of tetany, saved only by the implantation of the thyroid with its parathyroids obtained from a small monkey, and, one month later, of three parathyroids and a piece of thyroid the size of a small walnut, obtained one-half hour after death from the body of a man who had died of Bright's disease and uræmia. These tissues placed at once in normal saline solution at 32° F. (0° C.) were implanted successfully within an hour, the simian thyroid beneath the patient's sterno-mastoid, and the human thyroid and parathyroid beneath her left rectus abdominis, under chloroform anæsthesia. Danielsen⁶⁵ also

⁶² Erdheim: Brit. Med. Jour., July 21, p. 167, 1906.

⁶³ Von Eiselsberg: Centralbl. f. Chir., Nu. 21, 1909.

⁶⁴ Brown: Annals of Surgery, March, 1911.

⁶⁵ Danielsen: Beiträge z. klin. Chir., Bd. xxxvii, p. 998, 1910.

transplanted human parathyroids in a critical case with a successful result, and mentions 3 recorded cases.

An essential feature of parathyroid implantation is that the improvement may prove temporary only, *i.e.*, until, probably, the secretion the organ happens to contain is exhausted. This may last a couple of weeks and the symptoms return. It is only when the implanted organ assumes its normal functions *in situ* that cure occurs if the secretion produced is sufficient. Halsted's⁶⁶ valuable researches on the subject should be read by all operators in this class of cases.

That the oral use of parathyroid gland is of value in parathyroid tetany has been shown by MacCallum, Vassale, and others, though the first-named observer found that large quantities were necessary. Berkeley refers to other well-known observers, James, Putnam, and Halsted, as having obtained favorable results. In 2 cases recently reported by Bircher,⁶⁷ thyroid gland had first been tried, but without effect; parathyroid, however, caused prompt recovery.

An emulsion of fresh parathyroids may be given subcutaneously. Branham⁶⁸ reported a case thus treated successfully. Five fresh beef parathyroids were placed in a 1:1000 solution of bichloride of mercury and allowed to soak about ten minutes. The glands were cut, under strict asepsis, into 5 pieces under physiological salt solution. These pieces were placed in a mortar and ground into a homogeneous mass, 400 c.c. of sterile salt solution being poured into the mortar. This was then filtered through a sterile gauze and given as salt transfusion into the patient's breast. The oral use of thyroid and parathyroid extracts and the feeding of raw parathyroids had proved entirely useless. The recovery in this case, however, seems to me to be due to the fact that only one parathyroid was totally removed, and the three others only partly so, the remaining segments having eventually resumed their secretory activity. The injected emulsion thus acted as a palliative pending the functional recovery of what had been left of the organs. In Brown's case in which the parathyroids were removed, the

⁶⁶ Halsted: Amer. Jour. Med. Sci., vol. cxxxiv, No. 1, July, 1907, and Annals of Surgery, vol. xvi, p. 489, 1907.

⁶⁷ Bircher: Medizinische Klinik, Oct. 30, 1910.

⁶⁸ Branham: Amer. Jour. Med. Sci., vol. xlviii, p. 161, 1908.

benefit obtained from the emulsion lasted eleven days, and was then followed by violent tetany. Bircher's⁶⁹ 2 cases, also treated successfully with thyroid tablets, were probably of the same kind. Kocher^{69a} obtained recoveries "by energetically pushing the thyroid extract and iodothyrim in large doses." Biedl^{69b} urges that it should always be tried.

On the whole, what evidence there is tends to show that implantation of fresh glands should alone be depended on for a cure when the parathyroids have been destroyed.

Calcium lactate has been found efficacious by MacCallum and Voegtlin⁷⁰ and others. It may be given in 10-grain (0.66 Gm.) doses every hour or two, or in larger doses in saline solution per rectum, or in emergency cases, intravenously, 4 grammes (1 drachm) being given in 100 c.c. (25 drachms) of salt solution, as recommended by Winternitz,⁷¹ in a case of non-operative tetany. In Brown's case, however, calcium lactate, given orally, proved useless, as did all organic agents, including parathyroids, administered in this manner. The measures to prevent the spasms, the most active of which are chloral and the bromides, are reviewed in full in the articles on Tetany and Tetanus in the second volume.

The diet should receive considerable attention, and all substances rich in nucleins, including meats, should be strictly avoided, to reduce to a minimum the formation of spasmogenic wastes. A milk diet, farinaceous foods, and the free use of water to facilitate the elimination of what toxic wastes are formed are most useful in this connection. Exercise of any kind is also harmful, owing to the formation of muscular wastes that it entails. Rest in bed, or in an armchair, tends greatly to reduce the number and severity of the spasms.

PARALYSIS AGITANS.—This is a particularly interesting syndrome from the standpoint of physiology, for it clearly sustains the view that the thyroid and parathyroids are functionally united. Indeed, while Möbius, in 1883, found paralysis agitans associated with exophthalmic goiter, Lundborg, in 1891, met it in connection with myxedema, the autopsy show-

⁶⁹ Bircher: *Medizinische Klinik*, Oct. 30, 1910.

^{69a} Kocher: Quoted by Biedl, "Internal Secretory Organs," p. 50, 1913.

^{69b} Biedl: *Ibid.*

⁷⁰ MacCallum and Voegtlin: *Johns Hopkins Hosp. Bull.*, vol. xix, p. 91, 1908.

⁷¹ Winternitz: *Ibid.*, vol. xx, p. 269, 1909.

ing atrophy of the thyroid. These facts led both Möbius and Lundborg to connect the disease with the thyroid gland.

Various other phenomena, such as chronic rheumatism, arthritis, scleroderma, a brawny, or yellow-brown, pigmentation, hypothermia, etc., met with in cases of hypothyroidia, are also observed in paralysis agitans. In a case of mine the mask-like face of the latter disease recalled clearly that of an incipient case of myxœdema; Fraenkel had already observed myxœdematous areas. Parhon and Golstein⁷² found in the thyroid proper of a woman who had died of paralysis agitans what they term "manifest macroscopical and microscopical lesions"; Castelvì⁷³ found marked atrophic lesions in the thyroid gland in two instances, though Pasquier found none.

Conversely, many cases of paralysis agitans may suffer from the sensations of heat with cutaneous rise of temperature, and the abundant sweating commonly observed in exophthalmic goiter. The most suggestive case in this connection, however, is one reported by A. Gordon,⁷⁴ in which the characteristic attitude of paralysis agitans, the stiffness and fixation, the mask face and absence of expression, the propulsive movement and the tremor, coincided with goiter, some degree of exophthalmus, tachycardia, dyspnœa, and Graefe's sign of exophthalmic goiter.

There is ground, therefore, for the hypothesis that the genesis of paralysis agitans is in some way related to the thyroid apparatus. Yet, a suggestive feature of the problem is, that thyroid preparations are useless in these cases, as many observers, including myself, have ascertained. Again, the fact that, while the main phenomena of exophthalmic goiter are distinguishable in certain cases, in others those of myxœdema occur, serves further to obscure the problem. Moreover, while R. L. Thompson⁷⁵ examined fruitlessly the parathyroid of 9 cases in which death had been due to paralysis agitans for lesions, others, including Berkeley⁷⁶ and Allen J. Smith, referred to in paper by Camp,⁷⁷ found lesions in these glandules. Indeed, Lund-

⁷² Parhon and Golstein: "Les Sécrétions Internes," p. 218, 1909.

⁷³ Castelvì: *Rivista de medicina y cirugía practicas*, 1904.

⁷⁴ Gordon: *Proceedings of the Philadelphia County Medical Society*, Sept. 14, 1904.

⁷⁵ Thompson: *Journal of Medical Research*, Dec., 1906.

⁷⁶ Berkeley: *Old Dominion Journal*, April, 1909.

⁷⁷ Camp: *Jour. of the Amer. Med. Assoc.*, April 13, 1907.

borg⁷⁸ suggested, in 1904, that paralysis agitans was specifically the syndrome of hyperparathyroidia, a view to which Berkeley⁷⁹ was also led independently, in so far as disease of the parathyroids is concerned.

That the latter view is based on good ground is suggested by the fact that, while, as stated above, thyroid preparations are useless in paralysis agitans, active preparations of parathyroid favorably influence the disease. Moreover, their favorable action harmonizes with two established facts: that the parathyroids produce a powerful antitoxic substance, and that the pathogenic element of the disease is a long-recognized toxæmia. That symptoms of exophthalmic goiter and of myxœdema occur, does not weaken this position if the thyroid and parathyroids are united functionally. Nor does the presence of these two antagonistic disorders militate against the parathyroid theory, since we have seen that exophthalmic goiter lapses, if the patient lives long enough, into a myxœdematous state. Nor need we even deem Thompson's failure to find lesions in the parathyroids as defeating the Lundborg-Berkeley theory, for the functions of the parathyroids may be inhibited precisely as are those of the adrenals and thyroid, by lesions along the paths of the nerves through which their functions are governed. Hence the cases on record in which the causative lesion was found in various parts of the cerebrospinal system.

Suggestive also is the beneficial action of parathyroid. Berkeley⁸⁰ first employed commercial preparations; while good results were obtained in some instances, they often proved unreliable. He then used properly identified gland rubbed up fresh with milk-sugar into a dry powder, but found this also unstable. Subsequently he used the nucleoproteid solution referred to under the preceding heading as prepared by Beebe's method, and preserved with a few drops in the bottom of the container. This raised the therapeutic value of the product, but it was found to precipitate readily, and that it failed to bear prolonged transportation. His latest process is the following: The nucleoproteid extraction process (Beebe's method)

⁷⁸ Lundborg: *Deutsch. Zeitschrift für Nervenheilkunde*, "27," 1904.

⁷⁹ Berkeley: *Medical News*, Dec., 1905.

⁸⁰ Berkeley: *Medical Record*, Dec. 17, 1910.

is adhered to generally, but all the preliminary steps are hurried, and the precipitated nucleoproteid is not redissolved, but quickly dried in a draught of cold air; so that within eight or ten hours after the warm glands leave the bullock a minute amount of smooth yellow powder is obtained which stands physiologic tests admirably, is stable, easily handled, and does not require a freezing temperature (though for safety's sake it is recommended to keep it on ice). The powder is rubbed up with milk-sugar as a menstruum, and is placed in sealed containers.

A large proportion of the patients slowly respond to the treatment, though in about 25 per cent. the response is only temporary and imperfect. The rest showed progressive benefit during the entire period of treatment. The dose of nucleoproteid, as previously stated, is about 20 drops (1.23 c.c.) per day, while that of the glandules proper is 5 to 8 per day. The preserved gland is also given in capsules containing each the equivalent of $\frac{1}{2}$ grain (0.033 Gm.) of fresh gland, 5 to 7 of these being given daily. Parhon and Urechia⁸¹ and Delille,⁸² and others, have also reported considerable improvement, though the rigidity did not seem to be influenced.

ADRENAL OPOTHERAPY.

The prevailing view that adrenal preparations merely cause an ephemeral rise of blood-pressure and increase the vascular tone has greatly limited the intelligent use of these agents, though their empirical employment has somewhat compensated for this, and clinical applications have thus been discovered which the limited field of laboratory experimentation would never have brought to light. As we have seen, however, the adrenals are endowed with far more important functions, from my viewpoint: (1) their secretion takes up the oxygen of the air in the pulmonary alveoli and carries this gas to the tissue as constituent of the hæmoglobin; (2) it sustains, as such, oxidation, *i.e.*, metabolism, of the tissues (the latter having been sensitized for this purpose, we have seen, by the thyriodase).

⁸¹ Parhon and Urechia: Soc. de Neurol., Nov. 7, 1907.

⁸² Delille: L'hypophyse et la médication hypophysaire, p. 136, 1909.

While this conception sustains the present interpretation, it accounts for clinical phenomena which had not previously been explained, witnessed in the use of adrenal preparations. It shows, we have seen, that the rise of temperature noted by Morel, Lépine and the concomitant rise of temperature and increased metabolism noted by Oliver and Schäfer are due to increased oxidation. It accounts also for the rise of blood-pressure, since increased metabolic activity—excited directly by the adrenal principle besides that due to general oxidation—of the muscular coats of vessels is manifested by contraction, and, therefore, by elevation of the blood-pressure. The increased power of the heart is the obvious outcome of increased metabolism in the myocardium, precisely as it is in the vascular muscles, while the slowing of its action is due to the greater diastolic expansion that attends increased functional vigor and the greater resistance the blood-column offers as a result of the increased blood-pressure.

The preparation most used is the *glandulae suprarenales siccae*, or dried adrenal gland, of the U. S. P. It is best given in capsules in doses of from 2 to 4 grains (0.13 to 0.26 Gm.).

Epinephrin, adrenalin, and other active principles of the gland are not reliable when given orally, being often oxidized in the stomach and intestines, and rendered inert. But they are absorbed from the colon.

They may, however, be injected subcutaneously in 10- to 20-minim (0.62 to 1.23 c.c.) doses in small (1 to 2 drachms—1 to 8 Gm.) or large (1 to 2 pints—500 to 1000 Gm.) quantities of warm saline solution, the smaller quantity of the latter being preferable when repeated doses are necessary, absorption being very slow. It causes pain and, sometimes, general pallor when the injections are repeated; this is due to the general effect of the drug on the arterioles, which are also contracted temporarily.

When prompt results must be obtained, as in the treatment of shock, cardiac failure, etc., the intravenous method is preferable, injecting slowly 10 to 20 drops (0.62 to 1.23 c.c.) in a pint or quart of hot (108° F.—42° C.) saline solution. Or, 5 to 10 minims (0.3 to 0.6 Gm.) in 2 drachms (8 Gm.) of saline solution may be injected drop by drop into a vein, using a hypodermic syringe in an emergency.

The local application of an adrenal principle, adrenalin, epinephrin, etc., causes such marked contraction of the vessels that their lumina, when applied over small vessels, may become obliterated, thus arresting totally the flow of blood. The tissues become very pale, therefore, and even blanched, owing to the active metabolic activity set up in the vascular walls, and particularly their muscular elements.

The disorders in which adrenal preparations are indicated are numerous; but the majority of those in which they are of greatest value have already been considered, viz., *Addison's disease* (page 97) and *terminal hypoadrenia* (page 109), which in itself includes practically all febrile infections. A few others, however, may be considered here.

SURGICAL DISEASES.—Laboratory and clinical experience tend increasingly to show that man is more susceptible to the action of adrenalin than animals. While a subcutaneous injection of 1 drachm (4 c.c.) of a 1:1000 solution will hardly affect a rabbit, one-third of that quantity has produced untoward effects in normal as well as in tuberculous subjects (Souques and Morel), *e.g.*, vertigo, nausea, vomiting, severe pain under the sternum similar to that of angina pectoris, and a feeling of constriction about the chest, a rapid pulse, dyspnoea, cold sweats, and coldness of the extremities. Hypodermic doses of $\frac{1}{120}$ grain (0.00055 Gm.), however, are well borne. Intoxication may follow the use of adrenalin when injected into cavities such as the vagina, the rectum, the urethra, when the mucous membrane is abraded, lacerated, or denuded, thus rendering its absorption possible. The urethra seems to be particularly sensitive in this connection, the passage of bougies for stricture having caused poisoning in a number of cases. According to Braun,⁸³ the toxicity of epinephrin or other adrenal principles varies with the individual, but, in all, the danger lies in the use of concentrated solutions. He employs a solution of 0.64 Gm. (10 grains) of suprarenin borate in 100 c.c. (25 drachms) of 0.5 per cent. novocaine made up fresh from tablets for each operation; 125 c.c. (31 drachms) of this solution can be used without danger.

⁸³ Braun: Zelt. f. Gyn.; Amer. Jour. of Obstet., 1909.

Local applications may also be followed by untoward effects in the tissues to which adrenalin solutions are applied. Repeated applications, especially with the atomizer, of anything but weak solutions (1:10,000) to the nasal cavities or pharynx may give rise to œdema of the nasal mucosa, the uvula, tonsils, or pillars of the fauces. This is ascribed by most writers to "violent vasomotor constriction of the blood-vessels" and the resulting "venous stagnation," but it is in reality a secondary result of these effects, *i.e.*, paresis of the arterioles and œdema of the tissues. In some instances they cause persistent sneezing and acute coryza accompanied at times by severe pain in the upper portion of the nasal cavities. Some cases have been reported in which even sloughing and gangrene of the mucosa occurred. Elderly subjects are prone to this complication, according to Neugebauer. Post-operative hæmorrhages are not infrequently noticed after the use of adrenalin, owing to relaxation of the severed vessels. In the larynx, adrenalin solutions cause an uncomfortable dryness by interfering with the formation of lubricating mucus. This is especially distressing to singers. In the eye their use in scleritis and other disorders may be followed by severe iritis. Instillations of a 1:1000 solution in the Eustachian tubes have given rise to violent pain in the middle ear, which was renewed whenever the remedy was thus administered. The use of adrenalin solutions in the form of spray, at least, is contraindicated in infections, owing to the danger of facilitating the entrance of pathogenic germs into the sinuses.

The toxic effects produced, however, are readily accounted for by the functions in oxidation, metabolism, and nutrition I attribute to the adrenal secretion. Tracing the course of events from start to finish, we have at first the effects of excessive metabolism in all tissues: in the cerebro-spinal system, excitement; in the muscles, tremor; in the kidneys, polyuria; in the myocardium, violent contractions (palpitations); in the muscular coats of the vascular system, a marked rise of the blood-pressure. The latter in turn aggravates the process by causing congestion and engorgement of the capillaries (which are not, like the arteries, provided with a muscular coat) of all organs, including the lungs, causing œdema of these structures and dyspnoea. As the contraction of the arteries proceeds, the aorta has to bear the

brunt of the centrifugal pressure, giving rise to marked sub-sternal pain. When it becomes such that the arterioles obstruct the circulation the lethal phenomena are initiated: the pulmonary circulation being impeded, oxygenation fails to occur; asphyxia follows, and, the myocardium receiving too little blood to sustain its contractile power, the heart, already hampered by the pulmonary congestion, ceases to beat.

After local applications the morbid effects are all the result of the action of the adrenal principle upon the vessels. The dryness caused by solutions sprayed into the larynx is due to deficiency of blood supplied to the acini and the resulting inhibition of their function. If this is kept up by repeated applications, the tissues, no longer nourished, may slough off, as has been noticed in the upper respiratory tract of aged subjects. The œdema observed in this location is not active, as it is in the lungs, but passive, *i.e.*, due to exaggerated relaxation of the vessels after the intense constriction to which the drug had subjected them. This applies equally well to post-operative hæmorrhage, and to the severe pain (due to passive congestion) in the middle ear after instillations in the Eustachian orifice.

Shock and Collapse.—The familiar influence of adrenal preparations on the blood-pressure and the rôle in tissue oxygenation I ascribe to them afford a self-evident explanation of the excellent action they have shown in the treatment of this condition, since they meet at once the two main morbid factors: low cardio-vascular tension and depression of the vital process. The latter effect is shown by the increase of body heat noted by Reichert, Lépine, Morel, and others.

Kinnaman, in a comprehensive study of the temperature relationship to shock, concluded that as shock increased in severity the most uniform and progressive factor was the fall in temperature. He states that "in one series [of cases] the fall in temperature was the sole cause of shock." The results of Crile with adrenalin in salt solution given very slowly and gradually for a considerable time thus find a normal explanation in my interpretation of the rôle of the adrenal secretion. He resuscitated animals in this manner—with simultaneous artificial respiration—fifteen minutes after all signs of life had ceased, and was able to keep a decapitated

dog alive over ten hours by this same procedure. That it was because the adrenal secretion is able to incite and sustain tissue metabolism, *i.e.*, the vital process itself, that such results were obtained seems obvious.

This applies not only to shock, but also to *surgical heart-failure, collapse* from hemorrhage, *asphyria*, and *submersion*. The adrenal principle (suprarenalin, adrenalin, etc.) promotes energetically, as a catalyzer and constituent of the hæmoglobin, the intake of oxygen and its utilization by the tissue-cells, including the muscular elements of the cardio-vascular system, and thus causes them to resume their vital activity. It should be very slowly administered intravenously, 5 minims (0.31 c.c.) of the 1000-solution to the pint of warm (105° F.—40.5° C.) saline solution. In urgent cases, 10 drops (0.62 c.c.) of supracapsulin or adrenalin in 1 drachm of saline solution can be used instead, and repeated at intervals until the heart responds. Artificial respiration hastens its effects.

The same remarks apply to the untoward effects of chloroform, which are also due to circulatory failure, with partial suspension of the vital process in the tissue-cells. Here a relatively large dose must be used, 30 minims (2 Gm.) of epinephrin, supracapsulin, or adrenalin in a pint of warm (108° F.—42.5° C.) saline solution intravenously. If injected very gradually it will excite the cardiac muscle by a direct action upon it before reaching the lungs, and cause it to resume its contractions. Kothe⁸⁴ has used this method successfully in 5 cases of cardiac failure following spinal anæsthesia. Too rapid injection causes cramp of the cardiac muscle and holds it in systole. Straub^{84a} found that a weak solution kept up the blood-pressure if injected slowly intravenously.

The simultaneous use of $\frac{1}{100}$ grain (0.00066 Gm.) of atropine, hypodermically, aids materially the resuscitation by causing the arterioles to resume their functional tone, and thus to re-establish the *vis-a-tergo* motion of the blood in the capillary system. The physical methods, rhythmical traction of the tongue, suspension, etc., must, of course, not be neglected.

Hæmorrhage.—In hæmorrhage from the pharyngeal,

⁸⁴ Kothe: *Therapie der Gegenwart*, p. 95, 1907.

^{84a} Straub: *Münch. med. Woch.*, June 27, 1911.

œsophageal, gastric, or intestinal mucous membrane, the mastication of adrenal substance, or the use of powdered adrenal substance in 5-grain (0.33 Gm.) capsules, arrests the flow, by causing active metabolism in the muscular elements of the arterioles of the mucosa and constriction of these vessels—the characteristic local action of the adrenal principle.

Its use in intestinal hæmorrhage was studied with considerable care recently by C. J. Wiggers.⁸⁵ His conclusions were as follows: 1. Large doses of adrenalin (0.05 to 0.1 mg.) cause a short preliminary increase in hæmorrhage, followed quickly by a decrease or cessation of bleeding. On account of the great preliminary loss of blood they are always contraindicated. 2. Small doses of adrenalin (0.01 to 0.025 mg.) cause little or no preliminary increase, but shorten the course of hæmorrhage. As they save the red blood-cells in every way they are therapeutically desirable. 3. The method of introducing adrenalin determines the effect of blood-pressure and hæmorrhage. No results are obtained by subcutaneous administration. By continuous intravenous injection of weak solutions a slight elevation of pressure can be maintained and hæmorrhage simultaneously checked. This can also be accomplished by intramuscular injection. 4. Adrenalin is not indicated in all intestinal hæmorrhages. The condition of the blood-pressure is the criterion for its use. In hæmorrhages of short duration when the pressure has not fallen to any extent, a judicious use of nitrites proves of more benefit than adrenalin. When the bleeding has been profuse, however, and a low pressure already exists, it becomes vital that hæmorrhage should be checked without further reduction of pressure. Adrenalin finds its use in this field. 5. The use of adrenalin should always be closely followed by blood-pressure observations. A dose sure to be below the safety limit should first be tried, and the pressure carefully estimated. If no rise occurs, gradually increasing doses may be injected until a slight elevation of pressure is present.

TOXÆMIAS.—It was noted long ago by Abelous and Langlois, Charrin, Oppenheim, and others, that adrenal extracts antagonized certain toxins and other poisons. This is due to the

⁸⁵ Wiggers: Archives of Internal Medicine, March 15, 1909.

participation of the adrenals in general immunity which I pointed out as far back as 1903, the specific action carried on by their secretion being that of amboceptor. Goldsieber^{85a} noted a marked diminution of adrenalin in the adrenals of subjects in which death had been due to an infection: pneumonia, puerperal meningitis, etc., thus showing that in all such processes there is abnormal activity of the organs, *i.e.*, an extraordinary output of adrenal secretion. Many clinicians are now using adrenal preparations to compensate for this loss. (See Terminal Hypoadrenia, page 109).

CANCER.—In both rats and mice, carcinomatous and sarcomatous neoplasms have been caused to disappear by injections of adrenin, while they also prevented the growth of cancerous grafts. Reicher^{85b} tried the same treatment in man. A sarcoma was reduced to one-third of its size, which third with the aid of X-rays and the high-frequency current was caused to disappear. Malignant lymphomata and a case of melanosarcoma were also favorably influenced. Injections of adrenalin around a tongue cancer also proved beneficial.^{85c 85d}

In personal inoperable cases adrenal gland seemed to prolong life by delaying the cachexia, especially when given with iron. Suggestive in this connection is that, in Reicher's words: "It is remarkable that during the treatments the patients increased much in weight—up to 14 pounds. There must be a constant anomaly of metabolism somewhere." I may recall in this connection that eight years earlier I had pointed out that the function of the adrenal secretion was to take up the oxygen of the air in the lungs and to sustain tissue oxidation, metabolism, and nutrition—thus accounting for the gain in weight Reicher noted. Ritchie^{85e} recently reported the disappearance of a skin carcinoma under local applications of the 1:1000 solution of adrenin.

The desensitizing action of adrenalin by cataphoresis has been found by Reicher and Lenz^{85f} to permit the use of nearly double the dose of X-rays.

^{85a} Goldsieber: Wiener klin. Wochenschrift, June 2, 1910.
^{85b} Reicher: Deut. med. Woch., No. 22, 1910, and Berliner klin. Woch., No. 20, 1911.
^{85c} Echtermeyer: Berliner med. Woch., Aug. 21, 1911.
^{85d} Holscher: Ann. des méd. de l'oreille, du larynx, etc., No. 7, 1912.
^{85e} Ritchie: London Lancet, June 23, 1912.
^{85f} Reicher and Lenz: Deut. med. Woch., Jan. 4, 1912.

CARDIAC DISORDERS.—Kothe,⁸⁶ Rothschild,⁸⁷ Crile,⁸⁸ and others have obtained prompt recovery (after all other means had failed in Kothe's cases) in surgical heart-failure from intravenous injection of adrenalin in saline solution. Mankowsky,⁸⁹ Bates,⁹⁰ Floersheim,⁹¹ Deeks,⁹² and Boy-Teissier⁹³ have urged the value of adrenal preparations in cardiac disorders accompanied by weakness, particularly when there is dilatation, cyanosis, or oedema. Voight^{93a} found 10 to 15 minims of adrenalin 1:1000 solution and 5-grain tablets of the gland valuable in cardiac dropsy and cardiac dyspnea.

In 1853 Brown-Séquard⁹⁴ found that the venous blood of the venæ cavæ contained some substance which contributed to the contractions of the heart. A contemporary promptly relegated this experimental fact to oblivion, by showing that carbonic acid, the only excitant credited to venous blood, failed to cause an exposed heart to contract. Had it not been for this misdirected experiment it is more than likely that Brown-Séquard, over fifty years before Oliver and Schäfer, would have discovered that, in Schäfer's words,⁹⁵ the adrenal extract produced "a powerful physiological action upon the muscular system in general, but especially upon the muscular walls of the blood-vessels, and the muscular wall of the heart." He would then, moreover, have reached the obvious conclusion to which I was subsequently led, that, inasmuch as the adrenal secretion passed by way of the adrenal veins to the inferior vena cava, it was inevitably carried to the right heart in the blood of this great channel, and that it was the adrenal secretion, therefore, which helped the heart to contract.

This explains the beneficial effects of adrenal preparations in adynamic heart disorders. Their active principle *via* the venæ cavæ excites *directly* the muscular elements of the right heart. Besides this, however, the entire cardiac muscle is also, from my viewpoint, excited *indirectly*. The adrenal

⁸⁶ Kothe: Centralbl. f. Chir., Aug. 17, 1907.

⁸⁷ Rothschild: Therapie der Gegenwart, June, 1908.

⁸⁸ Crile: Amer. Jour. Med. Sci., April, 1909.

⁸⁹ Mankowsky: Russian Arch. of path., Clin. Med. and Bact., March, 1898.

⁹⁰ Bates: Medical News, March 2, 1900.

⁹¹ Floersheim: New York Medical Journal, Oct. 6, 1900, and May 4, 1901.

⁹² Deeks: Montreal Medical Journal, Nov., 1901.

⁹³ Boy-Teissier: Arch. gén. de méd., Aug. 23, 1904.

^{93a} Voight: British Med. Journal, March 9, 1912.

⁹⁴ Brown-Séquard: "Experimental Researches Applied to Physiology and Pathology," p. 104, 1853.

⁹⁵ Schäfer: Loc. cit., vol. 1, p. 951, 1898.

active principle being carried by the venous blood from the heart to the pulmonary air-cells, it is added to that already in the blood, and becomes converted into the albuminous constituent of hæmoglobin, which, as we have seen, sustains oxidation. In this form it returns from the lungs to the left ventricle, with the arterial blood it has enriched, to be distributed to the body at large. When we recall that the first arteries given off by the aorta are the coronaries, whose branches supply the heart muscle proper, it becomes evident that the entire heart is the first to receive blood freshly laden with oxygen. On the whole, the adrenal secretion itself contributes to the heart's working power in two ways: (1) by enhancing directly the contractile power of its right ventricle, and (2) by sustaining oxidation and metabolism of the entire cardiac muscle.

Emphasis must be laid upon an important practical fact in this connection, namely: that the obvious purpose of the direct aid the right ventricle receives from the adrenal secretion is to assist the walls of this ventricle in projecting the venous blood into the lungs. This explains the rapidity with which cardiac dyspnoea is relieved by adrenal preparations; they not only restore to the right ventricle its power to drive the venous blood adequately to the air-cells, but they supply it with the pabulum which enables it to absorb from the air enough oxygen to restore the general respiratory equilibrium. The increased metabolic activity in the vascular muscles being also enhanced, passive œdema is also caused to disappear, while the dilated heart tends to resume its normal dimensions.

Whether given orally, hypodermically, or intravenously, therefore, adrenal gland, through the agency of what active principle it happens to contain, enhances the contractile power of the heart. Mankowsky⁹⁶ found that its efficiency was best shown in cardiac weakness and threatening collapse, and all evidence available points in the same direction. Floersheim states that when powdered adrenal is placed on the tongue, mixed with saliva and masticated thoroughly, its effects appear within ten seconds. At other times it takes ten minutes to regulate a

⁹⁶ Mankowsky: *Russian Archives of Pathology*, March, 1898.

weak, irregular pulse, but the usual time has been between two and three minutes.

The dried gland in daily doses of $1\frac{1}{2}$ to 3 grains (0.1 to 0.2 Gm.) is used in Europe. Whether our preparations are weaker or not I cannot tell, but the fact remains that such doses have not proven active in my practice, 2 grains (0.13 Gm.) three times daily, when a good preparation is available, being necessary to obtain appreciable effects, *i.e.*, such effects as can readily, and with more accuracy, be obtained with digitalis. Kothe⁹⁷ injects 20 drops (1.23 c.c.) of the 1:1000 solution of epinephrin in 1 quart of saline solution intravenously. John⁹⁸ injects slowly, in the same manner, 3 to 15 minims (0.18 to 0.92 c.c.) of suprarenin in $1\frac{1}{2}$ drachms (5.55 c.c.) of saline solution. It has been used subcutaneously in 15 (0.92 c.c.) or more minims in $\frac{1}{2}$ to 1 pint (250 to 500 Gm.) several times daily if necessary by Josué and others. Netter gives 10 to 20 drops (0.62 to 1.23 c.c.) or more by the mouth, but also subcutaneously in saline solution, when larger doses are required.

The contraindications are mainly: chronic nephritis, aortic lesions with tendency to anginal pains, angina pectoris, and arteriosclerosis, in all of which conditions a marked increase of the vascular tension would be harmful.

The indications of adrenal preparations are, as stated, those in which weakness of the myocardium exists, though I would fear their use when degeneration is present, owing to the marked increase of vascular tension they cause, and the greater resistance thus imposed upon the heart. Their value is manifest where marked and threatening cardio-vascular adynamia exists, and in cardiac collapse in the course of infections, which is due, as I have shown under "terminal hypoadrenia," to arrest of adrenal functions. In such cases, especially where urgency prevails, adrenal medication promptly restores the arterial tension; the cardiac beats become more ample and regular, and the—perhaps suspended—pulse resumes its normal strength and rhythm.

In the treatment of valvular and other cardiac disorders, digitalis is more reliable, and it can be adjusted to the needs of each case with greater precision.

⁹⁷ Kothe: *Therapie der Gegenwart*, p. 95, 1

⁹⁸ John: *Münch. med. Woch.*, p. 1221, 1900.

RESPIRATORY DISORDERS.—We have seen that adrenal preparations enhance the vigor of the cardio-vascular contraction. The asthma often met with in elderly people is thus promptly relieved by these agents. This applies also to true asthma, as first shown by S. Solis-Cohen.⁹⁹ This result is explained, from my viewpoint, not only by the increased oxygen intake and the improved tissue oxidation just mentioned, but also by the more perfect hydrolysis of the toxic wastes to which the spasm of the bronchial muscles, and therefore the asthmatic paroxysms, are due. This introduces, however, an important feature of the problem, to wit, the participation of the whole organism in the improved oxygenation.

The prompt arrest of a paroxysm of asthma by the hypodermic injection of 5 to 10 drops (0.31 to 0.62 c.c.) of the 1:1000 solution of adrenalin chloride, first recommended by Kaplan, has been termed "inexplicable" and "marvelous"; but if the adrenal principle is considered as the active factor in general oxidation, and it is recalled that, according to Takamine, one two-hundred-thousandth of a grain (0.00000033 gm.) of adrenalin (and this applies as well to other adrenal principles, such as suprarenalin, epinephrin, etc.) suffices to awaken physiological action, one can readily understand why many times this dose will produce therapeutic effects. Especially does this assert itself when we take into account a fact I have long urged, to wit, that we must look upon the active principle of the adrenal secretion not merely as a reducing agent, but as a *catalyzer* which, though remaining itself stable, can take up oxygen and transfer it with extreme rapidity, and in relatively enormous quantities, to the hæmoglobin, and from this compound to the tissue-cells. The adrenal active principle has not only been found in the red corpuscles by Mulon, as we have seen, but its catalytic action, first pointed out by Poehl, meets precisely the conditions deemed necessary by Moritz Traube, in 1858, to explain the massing of oxygen in the tissue-cells through its all-powerful catalytic action.

It has been noticed that a rise of blood-pressure does not always occur when epinephrin or adrenalin is injected into the tissues, but this is due to its slow absorption, though the asth-

⁹⁹ Solis-Cohen: Jour. Amer. Med. Assoc., May 12, 1900.

matic paroxysm is aided at once. The rise of blood-pressure is hastened, according to Miles and Mülleberg, when the area in which the remedy was injected is massaged. Spraying the nose with a 1:4000 or stronger solution of adrenalin or suppositories containing this agent has also been found capable of arresting paroxysms of asthma by Matthews. Aronsohn applies to the nostrils an ointment of vaselin and lanolin, of each, 1 drachm (4 grammes), containing 30 to 60 minims (1.85 to 3.7 c.c.) of 1:1000 solution of adrenalin chloride. Weiss^{99a} recommends an injection of adrenalin $\frac{1}{80}$ grain and pituitary extract $\frac{2}{3}$ grain in 15 minims of water. A second injection was required in only 10 out of 300 cases.

In hay fever the nasal spray referred to above was, at one time, used extensively, but it eventually proved more harmful than beneficial. By exhausting the contractile power of the nasal mucosa it caused the latter to relax and to block the respiratory area. If used at all, it should be only for a short time. Matthews^{99b} uses a 1:1000 solution in severe cases and 1:2000 or 1:4000 in milder ones. Far more efficient is the adrenalin ointment 1:1000, to reduce the turgescence of the nasal mucosa, keeping the latter down by means of a 10-grain to the ounce of liquid petrolatum spray, between times.

Solomon Solis-Cohen recommends the use of adrenalin tablets, beginning with $\frac{1}{50}$ -grain (0.00132 Gm.) doses, and increasing the latter, if need be, as the patient becomes accustomed to the use of the remedy until $\frac{1}{10}$ grain (0.0066 Gm.) is given. The tablets are allowed to dissolve on the tongue. If the patient can remain in a dark room to avoid the reflex excitation of the sensitive centers, the remedy is given less often.

ASCITES AND OTHER EFFUSIONS.—In this condition, there is a more or less great loss to the circulatory blood of its adrenal principle, owing to the accumulation in the peritoneal cavity of a more or less great volume of its serum. The latter being, as I have shown, the intermediary between the red corpuscles and the tissues for the transmission of the adrenoxidase to the latter, the ascitic fluid deprives the body of part of its oxidizing principle, *i.e.*, transfers a given proportion of it where it cannot carry on its normal functions. In some cases, in fact,

^{99a} Weiss: Deutsche med. Woch., Sept. 19, 1912.

^{99b} Matthews: British Med. Jour., Feb. 19, 1911.

as in one recently observed by Bean,¹⁰⁰ the serum may be bloody. The marked anæmia and asthenia which complicate these cases speak in favor of this view.

That, in addition, the adrenal principle should prove useful in these cases, suggests itself, since they would restore to the organism that which is so essential to its physiological welfare. Fleischer and Loeb¹⁰¹ found that injections of adrenalin not only improved the general condition, but also that they increased the rapidity of absorption of the fluid from the peritoneal cavity. Tyson and Jump¹⁰² resorted to this measure in 3 cases. In the first patient ascites was due to chronic parenchymatous nephritis associated with moderate regurgitation at the mitral valve. Tapping had already been performed three times. Nine injections of adrenalin chloride were then given in the space of about two weeks, the original dose used being 7½ minims (0.5 c.c.) of a 1:1000 solution, rapidly increased to 30 minims (2 c.c.). The first 5 injections were given on successive days. After the third injection the line of dullness in the abdomen began to descend, and after the sixth ascites was barely demonstrable. The patient had two attacks of pulmonary œdema during the treatment, but stated that he had had previously several such attacks. The quantity of urine passed gradually rose during the treatment, the daily output at its termination being from 70 to 80 ounces (2100 to 2400 c.c.). Progressive improvement followed. As to the question whether the adrenalin had some influence upon the kidneys in addition to that on the absorptive power of the peritoneum, the fact that the patient had already been under treatment for a long time, which treatment had apparently been beneficial, leads to a conclusion in the negative.

The third patient was suffering from an abdominal carcinoma, probably arising in the stomach and extending to the omentum. The first injection of 30 minims (2 c.c.) apparently diminished the amount of fluid. The injections were gradually increased to 60 minims (4 c.c.), 12 in all being given, after which, no improvement being noted, paracentesis became necessary. The character of the causative disorder, however,

¹⁰⁰ Bean: *Chicago Medical Times*, Sept., 1910.

¹⁰¹ Fleischer and Loeb: *Jour. Exper. Med.*, vol. xii, No. 3, 1910.

¹⁰² Tyson and Jump: *Therapeutic Gazette*, Jan., 1911.

could but defeat the curative value of the adrenal principle. In Bean's case, from which nearly sixty gallons of fluid, sanguinolent at times, we have seen, complete recovery occurred.

Satisfactory results have also been obtained in serous effusions in the pleura and tunica vaginalis after aspiration, by injecting into the cavity from 8 minims (0.5 c.c.) to 2 drachms (8 Gm.) of adrenalin in four times the quantity of saline solution.

GENERAL INDICATIONS OF ADRENAL PREPARATIONS.—The list of disorders in which adrenal preparations have been, and are being, employed could be greatly extended, but I have limited myself to those in which their use has proven advantageous in the hands of a sufficiently large number of practitioners to warrant their being added to our trusted remedial agencies. In a certain number of diseases they may even be said, interpreted from my viewpoint, to exceed other means at our disposal in value. These are:—

1. Addison's disease. In this affection adrenal preparations compensate for the deficiency of adrenal secretion, and, therefore, for deficient general oxidation, metabolism, and nutrition. The dosage should be adjusted to the needs of each case. Beginning with 3 grains (0.2 Gm.) of the desiccated extract three times daily after meals, the dose should be gradually increased until the temperature and the blood-pressure become normal, when the last dose should be maintained. (See page 103.)

2. Surgical heart-failure; collapse from hæmorrhage, shock, asphyxia, and submersion. Here the adrenal active principle (suprarenalin, adrenalin, etc.), as a catalyzer and a constituent of the hæmoglobin, promotes energetically the intake of oxygen and its utilization by the tissue-cells, including the muscular elements of the cardiovascular system, and thus causes them to resume their vital activity.

3. The toxæmias, including bacterial infections, surgical septicæmias, etc., when collapse threatens, especially when a persistently low blood-pressure, hypothermia, and cyanosis are present. Besides enhancing pulmonary and tissue respiration, the adrenal principle, administered in the same way, enhances the efficiency of the immunizing process. (See pages 113 and 124.)

4. Capillary hæmorrhage from the pharyngeal, œsophageal, gastric, or intestinal mucous membrane. The mastication of tablets of adrenal substance, or the oral use of powdered adrenal substance in 5-grain capsules, arrests the flow by causing active metabolism in the muscular elements of the artèrioles of the mucosa and constriction of these vessels.

5. Asthenic cardiac disorders with dilatation of the right ventricle, dyspnœa, and possibly cyanosis and œdema, owing to the direct action of the adrenal principle on the right ventricle and improved oxidation and metabolism in the cardio-vascular muscles and the tissues at large. Tablets of from $\frac{1}{2}$ to 2 grains (0.033 to 0.13 Gm.) of the desiccated gland can be taken after meals.

6. Asthma, to arrest the paroxysms, by augmenting the pulmonary and tissue intake of oxygen and the cardio-vascular propulsion of arterial blood. From 5 to 10 minims (0.31 to 0.62 c.c.) of the 1:1000 solution of suprarenalin or adrenalin in 1 drachm of saline solution should be injected, drop by drop, into a superficial vein, or hypodermically.

7. To prevent the recurrence of serous effusions in the pleura, the peritoneum, the tunica vaginalis, etc., after aspiration, by reducing the permeability of the local capillaries and restoring the circulatory equilibrium.

8. In neuralgia or neuritis, as pointed out by Carleton, applied to the cutaneous surface over the diseased area to produce ischæmia of the hyperæmic nerves and thus arrest the pain. One to 2 minims (0.12 c.c.) of a 1 to 1000 adrenalin ointment should be applied by inunction.

PITUITARY ORGANTHERAPY.

I have submitted elsewhere in this work the many reasons which have led me to differ from those who consider the pituitary body as a secreting gland, and to attribute to this organ the functions of a composite nerve-center. Pituitary organotherapy, though of marked value, does not mean to me, therefore, as did the organic preparations reviewed so far in the present chapter, the scientific use of a substance which carries on well-defined functions in the body, but rather the use of a

tissue rich mainly in *chromaffin substance* and nucleins, or at least in substances capable of producing jointly the effects of adrenal preparations (a generally recognized fact) modified, and indeed improved, through their combination with other components of the pituitary body. I may recall in this connection that of the two lobes, as shown by Howell, Silvestrini, Thaon,¹⁰³ and others, the posterior is the only one whose extracts are active therapeutically, but that, as shown by Crowe, Cushing, and Homans,¹⁰⁴ it is not removal of this lobe which causes death in animals—as it should, were it like the adrenals and the thyroparathyroid body, a secreting gland important to life—but removal of the anterior, which therapeutically is inert.

What explanation of the rôle of pituitary preparations I will offer, therefore, will not take the so-called secretion into account; it will utilize the only certain fact we have at our disposal for this purpose, viz., that, as shown by Wiesel, the posterior lobe is rich in chromaffin substance—the active component of adrenal tissue—and that it is mainly the physiological effects of this substance—though advantageously modified as a therapeutic agent through its combination with other constituents of the same tissue, I repeat—that we witness.

The phenomena awakened by pituitary are strikingly those of adrenal preparations. Mairet and Bosc¹⁰⁵ found, in 1896, that subcutaneous injections of pituitary extract produced a rise of temperature which lasted but a couple of hours. An intravenous dose produced marked myosis, slowing of the respiration, powerful cardiac beats, and hyperthermia as main signs, the animals recovering, however. Schäfer and Vincent¹⁰⁶ then found that pituitary substance raised the blood-pressure—besides containing a depressor substance—and that this substance when applied to mucous membranes caused blanching, as is the case when a solution of adrenalin is applied. They also noted that in small mammals it caused, in toxic doses, paralytic symptoms which they also consider analogous to those caused by adrenal extracts. According to Jas. Barr,¹⁰⁷ pituitary extract actively produces

¹⁰³ Thaon: *L'hypophyse*, p. 99, 1907.

¹⁰⁴ Crowe, Cushing, and Homans: *Bulletin of the Johns Hopkins Hospital*, lay, 1910.

¹⁰⁵ Mairet and Bosc: *Arch. de physiol.*, p. 600, 1896.

¹⁰⁶ Schäfer and Swale Vincent: *Jour. of Physiol.*, p. 87, vol. xxv, 1899.

¹⁰⁷ Barr: *Lancet*, Nov. 13, 1899.

arteriosclerosis, and it is also known to produce glycosuria. In other words, it awakens all the typical phenomena, physiological and pathological, to which the adrenal product gives rise.

The marked advantage of pituitary—owing, doubtless, to the fact that it is bound up in organic combination with other components of the organ—is that it sustains the rise of blood-pressure to which it gives rise much longer than does adrenalin, thus being more reliable in shock and other emergency cases. It seems also to sustain the temperature and the muscular tone, cardiac, vascular, intestinal, and uterine, longer than the adrenal active principle. It possesses also a great practical advantage over adrenalin and other adrenal principles in that it can be administered by the mouth without compromising its effects.

A product called “pituitrin” by its manufacturers, in the form of a powder, is available on our market for oral use, the dose of which is given as 10 to 30 grains (0.66 to 2 Gm.). But this dose is too large, 5 to 10 grains (0.33 to 0.66 Gm.) being sufficient in most cases.

There is also a liquid extract of the posterior lobe, wrongly termed “infundibular extract,” the infundibulum being the pedicle which unites both lobes of the pituitary to the base of the brain. This infundibular extract affects mucous membranes precisely as do adrenal extractives, and should be applied only when diluted in eight or ten times the same quantity of saline solution. It may be given orally in 10- to 30- minim (0.62 to 2 c.c.) doses, or intramuscularly in 3- to 15- minim (0.2 to 0.92 c.c.) doses.

Another liquid preparation is also available, *i.e.*, “vaporole,” in small flasks containing 15 minims (0.92 c.c.) of a 20 per cent. extract, the quantity for one injection representing 3 grains (0.2 Gm.) of the posterior lobe, which contains the active agent. The injection should be given intramuscularly in the gluteal region, under strict antisepsis.

CARDIAC DISORDERS.—As shown by Rénon and Delille,¹⁰⁸ pituitary gland raises the depressed arterial tension and corrects purely functional disorders of rhythm.

It is recommended in doses ranging from 3 to 6 grains (0.2

¹⁰⁸ Rénon and Delille: *Soc. de Thérap.*, Jan. 22 and April 23, 1907, and *Congrès de Médecine de Paris*, Oct., 1907.

to 0.4 Gm.) of the whole gland, in myocardial weakness, particularly in that due to infections when the blood-pressure is receding, the pulse is becoming more rapid, and the urine scanty. While less active than digitalis as a diuretic, it nevertheless serves a valuable purpose in this connection. It is advantageous in mitral disorders when there is hyposystole and in chronic myocarditis, particularly that due to alcoholism. It is also useful in the tachycardia of certain neuroses and during menopause. These results have been confirmed by Trerotoli,¹⁰⁹ Parisot,¹¹⁰ and others.

It is contraindicated in aortic affections in any disorder in which high vascular tension prevails, and where there is a tendency to anginal pains, which it tends greatly to aggravate.

Pituitary gland is preferred to adrenal and particularly adrenalin, as stated above, when the action is to be sustained, the former being useful in urgent cases. Rénon and Delille, however, prefer digitalis, and recommend pituitary gland only when the latter fails. Leonard Williams,¹¹¹ on the other hand, deems it superior to digitalis, strophanthus, strychnine, and other classic tonics in what he terms the "runaway heart of toxic states," influenza, pneumonia, bronchitis, etc., with tachycardia, but low blood-pressure, and in all cases in which there is post-toxic cardiac debility. In these cases—which, from my viewpoint, are instances of pure hypoadrenia—Williams regards pituitary preparations superior to any remedy at our command.

In heart-failure and shock, it has been highly recommended by Mummery and Lymes and Bell and Wray, 15 minims (0.92 c.c.) of the extract being injected intramuscularly. While its virtues would seem to recommend it for the perpetuation of the effects of adrenalin, which are, at best, but temporary, the number of cases in which it has been tried has been too limited so far to warrant an opinion as to its actual value.

OBSTETRICS.—Dale¹¹² found experimentally that extract of pituitary caused "direct stimulation of involuntary muscle without any relation to innervation." Fröhlich and Frankl-Hochwart¹¹³ then ascertained that it caused contractions of the preg-

¹⁰⁹ Trerotoli: *Rivista critica di clinica med.*, Nos. 32 and 33, 1907.

¹¹⁰ Parisot: *Pression arterielle et glandes à sécrétion interne*, Paris, 1908.

¹¹¹ Williams: *Clinical Journal*, May 18, 1910.

¹¹² Dale: *Biochemical Journal*, 1909.

¹¹³ Fröhlich and Frankl-Hochwart: *Wiener klin. Woch.*, No. 27, 1909.

nant uterus in rabbits, while Foges and Hofstetter¹¹⁴ resorted to this property to check postpartum and other uterine hæmorrhages in 63 cases. The extract proved worthless by the mouth; but when injected intramuscularly, marked uterine contraction appeared within five minutes and lasted a long while in most cases. Voigts^{114a} found pituitrin most satisfactory in 60 cases; 1 c.c. (15 minims) sufficed. Pouillot and Vayssières^{114b} give 7½ minims intramuscularly several times daily in all adynamic or hemorrhagic conditions. Trapl^{114c} recommends it in placenta previa of the marginal type.

S. J. Aarons^{114d} found pituitary extract (vaporole) superior to ergot in labor cases. The uterus contracted better, more quickly, and more persistently than under ergot. It should not be used, however, until after completion of the third stage of labor, with the possible exception of certain cases of placenta prævia. The author gives brief histories of 11 illustrative cases. Among these is one of placenta prævia in which, after version and expulsion of the fetus, removal of the placenta was accompanied by profuse hæmorrhage. An intra-uterine douche of weak bichloride of mercury at 120° F. (48.9° C.) was given and pituitary extract injected deeply in the buttock; after this, there was no further loss and the uterus remained well contracted.

More recent clinical experience has, however, brought out some dangerous features. Nagy¹¹⁵ observed that it decreased the action of the fetal heart. Spaeth^{115a} had 2 cases of death in the newborn which are ascribable to this cause. Various authors have noted tetanoid spasm of the uterus. J. Clifton Edgar^{115b} states that both small and large doses have caused, through this defect, fatal compression of the fetus, premature separation of the placenta, and deep rupture of the cervix, his experience being based on 70 cases. In 39 of these in the first and second stages there were 2 and probably 4 still-births, and 3 instances of deep laceration requiring sutures to control the bleeding.

Pituitary extracts are evidently not safe agents in parturition. The author suggests, however, that the use of the extract in

¹¹⁴ Foges and Hofstetter: *Zeitschr. für Gynäk.*, No. 12, 1910.

^{114a} Voigts: *Deut. med. Woch.*, Dec. 7, 1911.

^{114b} Pouillot and Vayssières: *Presse médicale*, No. 4, 1913.

^{114c} Trapl: *Monats. chr. f. Geburtsh. u. Gynäk.*, Oct., 1912.

^{114d} Aarons: *London Lancet*, Dec. 24, 1910.

¹¹⁵ Nagy: *Zentralbl. für Gynecol.*, March 9, 1912.

^{115a} Spaeth: *Ibid.*, Feb. 1, 1913.

^{115b} Edgar: *New York Med. Jour.*, p. 150, July 19, 1913.

subinvolution be limited to cases with associated low blood-pressure.

Ott and Scott¹¹⁶ found infundibulin, *i.e.*, extract of the posterior lobe, to act as a powerful galactagogue in the goat. So far, however, it has not been tried in women.

INFECTIOUS DISEASES.—In this general class of disorders the use of pituitary acts, from my viewpoint, and in keeping with the effects of adrenal preparations, by enhancing the immunizing activity of the blood and the tone of the cardio-vascular system.

Rénon and Delille¹¹⁷ found that in typhoid fever it raised the blood-pressure, slowed the pulse, increased diuresis, and improved the patients in general, hastening convalescence noticeably. In diphtheria, in which the toxin reduces the vascular tension and promotes cardiac complications, it lowered the pulse-rate, raised the blood-pressure, and increased diuresis. In erysipelas it seemed to hasten the favorable evolution of the disease. In pneumonia it raised the blood-pressure when this became low, but without influencing favorably the evolution of the disease. In bronchopneumonia, however, the opposite proved to be the case, considerable benefit being noted. Influenza was found to be very favorably influenced, rapid recovery resulting in patients aged, respectively, 80 and 63 years. This was confirmed by Azam,¹¹⁸ in the infectious form. Rénon and Azam enumerate the phenomena which, in infectious diseases, indicate the need of pituitary: 1, a fall of the arterial tension; 2, quickening of the pulse and, as complementary minor phenomena, insomnia, anorexia, abnormal sweating, and heat flushes. Under the influence of pituitary there occur: 1, increase of arterial tension; 2, slowing of the pulse, with increase of power and amplitude; 3, increased diuresis; 4, increase in weight; 5, hastening of convalescence.

In several cases of tuberculosis treated by Rénon and Delille, the results were not, on the whole, encouraging. In a case of Addison's disease complicating tuberculosis, however, there was a notable rise of the blood-pressure and diminution

¹¹⁶ Ott and Scott: *Monthly Cyclopædia and Medical Bulletin*, Nov., 1910.

¹¹⁷ Rénon and Delille: *Bull. gén. de Thérap.*, Feb. 8, 1907, and Delille: *Loc. cit.*

¹¹⁸ Azam: *Jour. de méd. et de chir. pratiques; Practitioner*, March, 1908.

of the asthenia. Trerotoli had already noted the beneficial effects of pituitary body in Addison's disease—a fact which further suggests that the active agent of pituitary substance is its adrenal component.

ACROMEGALY.—The possible value of pituitary extracts in acromegaly, a disease of the pituitary body, has naturally suggested itself, but, although a few of the symptoms, the headache, lethargy, and amnesia, were relieved in some, no cures were obtained. This subject has already been referred to on page 607.

Analysis of the cases reported as benefited suggests an explanation of its mode of action, however, one quite apart from any functional relationship with the organ as the source of an internal secretion, but entirely in keeping with the presence in the pituitary preparation of adrenal secretion in organic combination. Marinesco¹¹⁹ observed that it was the extremely violent headaches that were relieved, there being no benefit otherwise excepting perhaps increased diuresis. Kuh,¹²⁰ obtaining no favorable result, withdrew the remedy, but the patient begged to be given the powders again, having found his headache much more intense when he failed to take them. The same observation had been recorded by Cyon,¹²¹ the patient, an obese child of 12 years, having besides lost twenty pounds in weight. What benefit was obtained in 1 case out of 7 cases treated by Kinnicutt¹²² was also limited to the headache and neuralgia. Leszynsky,¹²³ after a prolonged trial in 2 cases, wrote: "While some published reports as to the efficacy of the preparations of the sheep's gland have seemed quite encouraging in so far as the relief of headache and of paræsthesia of the hands is concerned, it is the general consensus of opinion that it in no way influences the progress of this disease."

Still, the relief of the headache and paræsthesiæ indicates some potent action. This is accounted for if the adrenal principle is considered as the active agent of pituitary preparations, since, as Langley has shown, it is principally upon the

¹¹⁹ Marinesco: *Semaine Médicale*, Nov. 13, 1895.

¹²⁰ Kuh: *Jour. Amer. Med. Assoc.*, Feb. 1, 1902.

¹²¹ Cyon: *Progrès Medical*, Nov. 26, 1898.

¹²² Kinnicutt: *London Lancet*, vol. II, p. 173, 1896.

¹²³ Leszynsky: *Medical Record*, June 30, 1900.

arterioles that the adrenal principle acts, a view which has now become classic. Such being the case, the tumor of the pituitary, or the compressed tissues around it, receive less blood through their constricted arterioles, and the sensory terminals of the peripheral likewise. The resulting ischæmia of these tissues thus accounts for the diminution of pain—as long only as the remedy is administered. ●

EXOPHTHALMIC GOITER.—Rénon and Delille¹²⁴ obtained considerable improvement in this disease by the use of pituitary gland. From the fourth to the fifth day, the sleeplessness, tremor, digestive disturbance, sweating, and sensation of heat were considerably lessened. The tachycardia improved less rapidly, the pulse becoming slower gradually and attaining its slowest rate toward the fifteenth day. The arterial tension also rises steadily, attaining the maximum toward the third week, falling again somewhat, but not to the former low level. Some diminution of the exophthalmus occurred, but the goiter was not reduced. The dose administered was $4\frac{1}{2}$ grains (0.30 Gm.) of the whole pituitary (ox) gland daily, a dose which they deem advisable to increase to $7\frac{1}{2}$ grains (0.50 Gm.) in divided doses daily. The symptoms tend to return, however, on discontinuing the remedy. Cases subsequently treated were also benefited, but no cures were effected.

This mode of action, from my viewpoint, corresponds precisely with that referred to under the preceding heading. We have seen in the fifth chapter that the main pathological condition, that to which all the prominent symptoms of exophthalmic goiter were due, was a general dilatation of the arterioles. Pituitary extracts causing constriction of these vessels as long as it is administered, it offsets for the time the morbid phenomena enumerated. That such is actually the case was demonstrated by Hallion and Carrion,¹²⁵ who found, experimentally, that pituitary extracts “always produced their effects by raising the arterial tension,” producing at the same time “an intense vasoconstrictor action upon the thyroid body.” Briefly, we have here precisely the physiological action necessary, the vasoconstrictor power of the adrenal component of

¹²⁴ Rénon and Delille: *Soc. Oesthérap.*, March 13, 1907.

¹²⁵ Hallion and Carrion: *Ibid.*

the pituitary gland superseding the vasodilator action of the thyroid, the underlying cause of the disease.

NERVOUS AND MENTAL DISEASES AND MYOPATHIES.—

Rénon and Delille used pituitary in 10 neurasthenics in whom tachycardia, irregular vascular tension, often below normal, a sensation of oppression, myasthenia, insomnia, and anorexia were present. In these cases, 3 to 5 grains (0.2 to 0.3 Gm.) daily proved remarkably useful, though no complete recovery was noted.

De'llille and Vincent¹²⁶ obtained a complete recovery in a grave case of bulbo-spinal myasthenia by the simultaneous use of pituitary and ovarian extracts. Parhon and Urechia and Léopold-Lévi and de Rothschild¹²⁷ had also obtained favorable results with pituitary in similar cases. Browning¹²⁸ observed good effects in cases of chorea in which this disorder occurred in conjunction with stunted growth, as shown under the next heading.

In epilepsy, it was tried by Mairet and Bosc,¹²⁹ but only served to increase the number of attacks—a result to be expected, since Spitzka has shown that these were due to abnormal elevation of the blood-pressure. In some instances it provoked delirium.

Sollier and Chartier¹³⁰ tried pituitary in mental disorders and found it useful in depressive states. It raised the blood-pressure, reduced the pulse, suppressed profuse sweating, and improved the asthenia. The synthesis of perceptions and the association of ideas were improved, and mental operations were incited more promptly.

STUNTED GROWTH AND IMBECILITY.—In the case of a child of 3 years, which had shown the evidences of hypothyroidia with idiocy sufficiently to suggest the use of thyroid, Léopold-Lévi and de Rothschild found this agent useless. The case being attended with marked myasthenia, they administered pituitary extract 1½ grains (0.1 Gm.) twice daily, which corresponded with 7½ grains (0.5 Gm.) of the fresh gland. Marked signs of improvement appeared within a few days. The intelligence

¹²⁶ Delille and Vincent: Soc. de Neurol., Feb. 7, 1907.

¹²⁷ Léopold-Lévi and de Rothschild: *Ibid.*

¹²⁸ Browning: New York State Journal of Medicine, Sept., 1909.

¹²⁹ Mairet and Bosc: Arch. de Physiol., p. 600, 1896.

¹³⁰ Sollier and Chartier: Congrès de Dijon, Aug., 1908.

developed to a remarkable degree, and soon reached that of a child of a corresponding age, 3 years, though before the treatment it did not exceed that of a 7 or 8 months' infant. Two similar cases, one of which showed symptoms of Little's disease, were similarly benefited.

Browning¹³¹ used pituitary only in undersized or backward children and youths (not real dwarfs or midgets). He gives the following histories:—

1. A frail, choreic girl of 14 years had made little or no recent advance in growth. On pituitary, with some accessories for the chorea, she gained a couple of pounds in weight and over an inch in height in three and a half months, the chorea disappearing. 2. A slightly rachitic boy of 2 years, after a period of cessation of growth, increased from 25 to over 30 pounds (*i.e.*, over 20 per cent.) in six months on the somewhat irregular administration of pituitary,—besides recovering in all ways, and keeping up his good progress since, though at a slower rate. Browning noted when growth is once started up in this way it usually keeps on satisfactorily. 3. A somewhat choreic boy of 13 years and of scanty physique received pituitary, besides at times arsenic and accessories. Although his growth was said to have been at a standstill previous to this, he gained 2 inches in height and 10 pounds in weight in the next eight months. In another ten months, on somewhat irregular continuation of the pituitary, he made a further gain of 3 inches in height and 11 pounds in weight,—when the father began to inquire anxiously for agents with the opposite effect. This is a record for a year and a half, of 5 inches in height and over 20 pounds in weight, the patient having been under 56 inches and 70 pounds at the start.

INTESTINAL PARESIS.—Bell and Hicks¹³² have found pituitary extract of value in paralytic distention of the intestines. It never failed either in post-operative or other paresis if given intramuscularly when the intestine begins to distend in 15-minim doses (0.92 c.c.) repeated in an hour, if required. The effect is then sustained by daily doses if need be. The beneficial influence of the injections was, as a rule, noticeable in a few minutes.

¹³¹ Browning: *Loc. cit.*

¹³² Bell and Hicks: *British Medical Journal*, March 27, 1909.

OVARIAN ORGANOTHERAPY.

As is well known, the ovaries correspond in many particulars with the testes in their influence upon development. Removal of the former prevents the normal development of the uterus and the appearance of menstruation, while their removal after puberty arrests menstruation and is followed by atrophy of the remaining structures of the genital apparatus. The whole organism is influenced by the ovaries, for their destruction or absence causes girls to grow without the general physical attributes of the female sex. This led Brown-Séquard to consider the ovaries as the source of an internal secretion. This view has been upheld by many observers who found that ovaries transplanted in the abdominal cavity, *i.e.*, elsewhere than in their normal location, restored to the other genital organs the power to develop and carry on their physiological functions. The identity of this supposed internal secretion and the manner in which it carries on its function have, however, remained obscure.

My own view, submitted at the beginning of this chapter, does not cover this feature: it refers only to the manner in which ovarian preparations produce their effects. It points out that these are similar to those awakened by adrenal substance, and that it is probably to the presence of this substance—not necessarily an internal secretion—in the ovaries that they must be attributed. There exists, as shown by Schäfer, a close homology between the interstitial of the ovary and the same cells in the adrenals; both sets of organs are derived from the Wolffian body; ovarian extract raises the blood-pressure and slows the heart, as shown by Fedoroff,¹³³ Jacobs,¹³⁴ and others. Removal of the ovaries, moreover, reduces the oxygen intake 10 per cent., as shown by Loewy and Richter,¹³⁵ while ovarian extract restores it; it has been, therefore, regarded as an oxidizing ferment. Neumann and Vas¹³⁶ noted that ovarian extract enhanced metabolism; Senator observed that ovarian preparations increased diuresis and the excretion of urea and phosphoric acid. Its physiological effects are those of adrenal preparations, therefore, in every respect.

¹³³ Fedoroff: *La Gynécologie*, Oct. 15, 1891.

¹³⁴ Jacobs: *Dublin Jour. of the Med. Sci.*, Sept. 1, 1897.

¹³⁵ Loewy and Richter: *Berlin. klin. Woch.*, Bd. xxxvi, S. 1095, 1899.

¹³⁶ Neumann and Vas: *Monats. f. Geburtsh. u. Gyn.*, Bd. xv, S. 433, 1902.

Its effects on oxidation are so striking, in fact, that they have been clearly recognized by many clinicians. "We are authorized to classify ovarian organotherapy among the oxidizing agents," write Dalché and Lépinos.¹³⁷ "This conclusion, it must be admitted, is that reached by several authors. Curatello and Tarulli believe that the internal secretion of the ovaries favors the oxidation of phosphorized organic substances, hydrocarbons, and fats. According to Gomes, it enhances oxidation and hydrolysis and favors the elimination of phosphates. . . . Albert Robin and Maurice Binet have shown that there is during menstruation an increase of the respiratory exchange. Keller, studying the general exchanges, found that there was increased nitrogen oxidation. We have ourselves found that menstruation, in itself, enhances vital functions and particularly the great function of general oxidation." Sauvé^{137a} states that ovarian extract increases the hæmoglobin content of the blood.

The *preparation* in general use is the desiccated gland, which may be given in doses of 2 to 5 grains (0.132 to 0.33 Gm.) twice daily. The fresh organ may be employed in 10- to 15- grain (0.6 to 1.0 Gm.) doses where the pharmaceutical product is not available. It soon loses its effect; small doses should first be given, then gradually increased.

Ovarian preparations have been tried in many disorders, but it is mainly in connection with those of the genital apparatus that they have been found of actual value.

NATURAL AND ARTIFICIAL MENOPAUSE.—In disorders occurring in the course of the physiological menopause, or when the latter is produced by bilateral oöphorectomy, ovarian preparations have proven of considerable value in a large proportion of cases since Brown-Séquard first introduced their use. Experience has shown, however, that the improvement lasts only as long as the agent is administered, and that, furthermore, certain phenomena: the palpitation, trembling, and "nervousness," disappear earlier than the others, *i.e.*, the asthenia, flushes, irritability, and psychoses, though effects in all symptoms, including the cutaneous disorders,—especially acne rosacea and eczema,—are promptly realized, sometimes as early as the fourth day.

¹³⁷ Dalché and Lépinos: Bull. gén. d. thérap., Jan. 8, 1902.

^{137a} Sauvé: Paris médical, April 1, 1911.

These effects are normally explained by the influence of the remedy on general oxidation and the improvement of the antitoxic functions of the blood, the imperfect hydrolysis of tissue wastes being the underlying cause of the phenomena other than the general asthenia.

The best results are obtained in young women who have grown obese after removal of the ovaries, or in whom obesity is due to ovarian insufficiency. In physiological menopause they are less marked, as a rule, and sometimes fail altogether to appear. In such instances, good results may sometimes be obtained by giving simultaneously 1 grain (0.066 Gm.) desiccated thyroid, or by depending upon the latter remedy alone. In congenital ovarian insufficiency, desiccated ovary has caused the appearance of menstruation.

W. E. Dixon,¹³⁸ of Cambridge University, recalls that the presence of ovarian tissue in the body, however small in amount, is sufficient to prevent the distressing symptoms which frequently follow complete extirpation; even transplanted ovaries are sometimes able to prevent the menopause attending removal of the ovaries. Hence the beneficial effects of ovarian preparations.

Of late, however, the general attention has been centered upon the therapeutic use of the essential structure of the ovary, the corpus luteum.

CORPUS LUTEUM ORGANOTHERAPY.

The consensus of opinion at the present time is that the internal secretion of the ovary is produced by the corpus luteum. The function of the corpora lutea in the early stages of their life is to initiate growth processes in the uterine cavity by means of this internal secretion and subsequently to preside over the nidation and development of the ovum, and the cyclic engorgement preceding menstruation. The recent labors of Fraenkel¹³⁹ confirming his previous investigations have strongly sustained the internal secretion theory and its controlling influence over the above functions. He found, moreover, that the therapeutic value of corpus luteum was limited to cases presenting symptoms of vasomotor origin due to absent or deficient ovarian activity.

¹³⁸ Dixon: Practitioner, May, 1901.

¹³⁹ Fraenkel: Archiv f. Gynäkologie, B. xci, S. 705, 1910.

This coincides with the earlier conclusion of J. G. Clarke¹⁴⁰ that the office of the corpus luteum was, among others, that of "a preserver of the ovarian circulation"—a fact which explains in turn the presence of adrenal-like tissue, whose secretion, as is well known, is eminently capable of sustaining vascular tone. Indeed, as is generally believed, it is the corpus luteum which produces the ovarian internal secretion; it should, in accord with what I have stated concerning the mode of action of the ovaries, also produce effects similar to those of adrenal preparations. We need but recall that in the adrenal hypernephroma of children one of the essential phenomena witnessed is the extraordinary development of the genital organs, those of a child of 5 years, for instance, being practically those of an adult. Bouin, Ancel, and Villemin¹⁴¹ found that the primary effect of toxic doses of lutean extract was a violent elevation of the blood-pressure, sufficient to produce effusion into all serous cavities. The physiological effects of therapeutic doses have not been sufficiently studied to show positively, as was the case with the ovaries, that they are all those of adrenal preparations, though what there is known points in that direction. One fact is certain, however, viz., the functions of the organ should not be ascribed to its internal secretion; its mission is probably limited to that of sustaining the circulation of the ovarian circulation, as pointed out by J. G. Clarke.

The *preparations* available include desiccated corpus luteum (*glandulae lutei desiccatae*), which may be given in 3- to 5-grain (0.2 to 0.3 Gm.) doses three times daily. It is usually administered before meals, but if, as is sometimes the case, it causes gastric disturbances it may be administered during, that is to say, in the course of, the meal. The term "lutein" is sometimes applied to the same product, but it is misleading, and its use should be discouraged.

The indications for desiccated luteum are similar to those for ovarian preparations.

NATURAL AND POSTOPERATIVE MENOPAUSE.—It must be said that the evidence as to the therapeutic value of desiccated luteum is, to say the least, conflicting. Morley,¹⁴² who supplied

¹⁴⁰ Clarke: Johns Hopkins Hospital Report, vol. II, No. 4, 1898.

¹⁴¹ Bouin, Ancel, and Villemin: Nouveaux Remèdes, March 8, 1907.

¹⁴² Morley: Jour. Mich. State Med. Soc., Nov., 1909.

desiccated luteum to ten physicians, and obtained reports of its use in 18 cases, 14 of which suffered from postoperative menopause, and 4 from natural menopause, states that 5 were cured, 12 improved, and that but 1 failed to be relieved.

C. A. Hill¹⁴³ also reported results obtained with extract of corpora lutea in 12 patients, ranging in age from 25 to 38 years, who showed the most severe type of nervous symptoms after removal of both ovaries. The "nervousness" was completely relieved by the treatment in each case. In only 2 cases, however, was there complete relief from flashes of heat. In another case, suffering from insomnia, which had continued ever since the operation over a year before, and was uninfluenced by hypnotics, complete relief was attained after the use of 50 5-grain (0.33 Gm.) capsules. One case reported an increase in sexual desire, while in the remainder no noticeable change was experienced. No complete cures were obtained. Several cases had interrupted treatment only, and others, who ceased treatment, were compelled to resume owing to return of symptoms. The preparation in each case was given in 5-grain (0.33 Gm.) capsules three times daily, one-half to one hour before meals.

On the other hand, Ellice McDonald¹⁴⁴ publishes a report of 20 personal cases in which he had used a similar preparation. "The results of this study, small though they be, extending over five years," writes this observer in his conclusions, "seem to indicate that the control of surgical menopause need not be sought in the corpora lutea. Its value is in cases in which the uterus and ovaries or uterus alone are retained. Particularly is it valuable in the treatment of scanty menstruation and the premature menopause. I have treated a number of cases at the outdoor dispensary of the Kensington Hospital for Women, with extract of the whole ovary, and never saw any definite results therefrom. But the lutein extract, being the essential part of the ovary, does seem to help in some degree and should be accompanied, in suitable cases, by dilatation of the uterus, with the use of the stem pessary following operation, as advised by Manson. At least, administration of lutein is indicated after operations on pregnant women in whom miscarriage is feared.

¹⁴³ Hill: *Surgery, Gynecology, and Obstetrics*, Dec., 1910.

¹⁴⁴ McDonald: *Jour. Amer. Med. Assoc.*, July 16, 1910.

This is particularly true in the early weeks of pregnancy during the imbedding of the ovum, as it has been shown experimentally that the corpus luteum has a definite effect under such circumstances."

It is obvious that the clinical experience at our disposal is still too limited to warrant any decision as to the actual value of corpus luteum, though it must be said that many desultory cases have been published in which its use was extolled. McDonald rightly lays stress on the facts that "the manifestations of the surgical menopause are too varied and extreme to allow explanation by the mere absence of the internal secretion of the ovary. The internal secretion of the ovary is but a factor in the process of the menstrual life."

I would go one step further and express a doubt that we are dealing at all with an "internal secretion," a designation applied to almost any organic juice nowadays, and reiterate what I say elsewhere, viz., that true internal secretions are fewer than is generally believed.

ORCHITIC OR TESTICULAR ORGANTHERAPY.

From the standpoint of therapeutics, testicular preparations can hardly be regarded as of more than historical interest. The influence of the testicles on the body at large is well known. Castration influences the development of the organism in many particulars. Eunuchs preserve to a certain extent the characteristics of infantilism, the skin remaining soft and white, their muscles flabby and weak, and the voice high pitched. Yet they are usually tall, owing to inordinate growth of the bones. They lack courage, initiative, and intelligence. It is evident, therefore, that the testicles do not carry on genital functions only. Brown-Séquard taught that they carried on a dual rôle: 1st, procreation; 2d, the production of an internal secretion which stimulates and sustains the energy of the nerve-centers and cord, and capable, moreover, of endowing the individual with physical, moral, and intellectual characteristics of sex. His own physical and intellectual activity having been greatly improved at the age of 72 years, by injections of an extract prepared from the testes of young dogs, he concluded that it

possessed marked therapeutic value. No one who, as I did, saw Brown-Séquard before and after he had submitted himself to this treatment could stretch his imagination sufficiently to attribute the change in his appearance to auto-suggestion. He literally looked twenty years younger.

The prevailing opinion is that the beneficial effects obtained from testicular preparations are not due necessarily to an internal secretion, though the existence of such is not denied, but to nucleo-albumins, substances that are rich in phosphorus, resembling greatly lecithins and glycerophosphates.

As previously stated, the testicular active principle, spermin, from my viewpoint, is, or at least corresponds with, as to its physiological action with the adrenal principle. We have seen that the latter sustains oxidation and metabolism. Batty Shaw,¹⁴⁵ unaware of any such connection, writes: "Spermin possesses the very curious property of being an oxygen carrier, and, according to Poehl, is responsible for those internal oxidations which take place in the body tissues." Again, I have urged that the adrenal secretion carries on its oxygenizing function catalytically as a ferment. Pantchenko¹⁴⁶ states that "Spermin acts catalytically, thus increasing the oxidizing power of the blood, and simultaneously activates the intra-organic oxidation processes where these are weakened." Moreover, as is the case with the active adrenal secretion, spermin gives, according to Mari, the guaiac and Florence hæmin test—which consists in adding a drop of iodine-potassium iodide solution to the fluid obtained by soaking a seminal stain in water. At the point of contact of the two drops, dark-brown needle-shaped or rhomboidal crystals will form which resemble the crystals of hæmin.

Dixon states that a constituent of orchitic extract is unaltered by boiling; McCarthy holds that it increases the force and regularity of the heart much as does digitalis. It enhances the resistance to disease, increases the production of urea, and also acts directly upon the cardio-vascular system. Moreover, as shown by Poehl—a fact which indicates that it is not specific

¹⁴⁵ Shaw: "Organotherapy," p. 205, 1905.

¹⁴⁶ Pantchenko: *Tribune médicale*, vol. xxvii, p. 11, 1896.

to the testis—it is a ubiquitous constituent of the whole organism, in the female as well as the male.

Testicular preparations, including spermin, have been recommended in a host of disorders, particularly tabes, neurasthenia, melancholia, impotence, and paralysis agitans; in several cutaneous disorders, eczema and psoriasis; in disorders of nutrition, gout, obesity, and glycosuria; but others again have failed to obtain any favorable results. Spermin has also been recommended by Poehl and his followers not only in the majority of the foregoing disorders, but in many others besides, in acne, rheumatism, syphilis, marasmus, and in various infections, such as typhoid fever, diphtheria, and even cholera. It has been tried in Addison's disease, but adrenal preparations are to be preferred.

In the light of the analysis submitted above, however, there is good ground for the belief that beneficial effects were obtained in all these maladies. That the nucleo-albumins of orchitic extract acting as would glycerophosphates could be beneficial in the disorders enumerated, no one can deny. This can hardly be said, however, of the cutaneous and nutritional disorders, unless the spermin the extract contains, by enhancing oxidation and the destruction of toxic wastes, proves to be the active agent. Spermin itself—as adrenoxidase—is unquestionably capable of doing this actively, and in syphilis and marasmus to markedly enhance the functional activity of all tissues. Again, the beneficial rôle of spermin in infections finds its explanation in a fact I have repeatedly emphasized, viz., that the oxygenized adrenal secretion, the active agent of spermin, from my viewpoint, is an active participant in all immunizing processes, local and general. The main point to determine, however, is whether orchitic extract, or spermin, affords better or as good results in any of the disorders enumerated than other remedies at our disposal. The evidence available indicates that such is not the case.

KIDNEY ORGANOTHERAPY.

That the kidneys produce an internal secretion is still problematic. Brown-Séquard, having removed the kidneys and caused uræmia, found that the injection of a glycerin extract of

kidney prolonged the life of the animals as compared to those in which the same operation was not followed by the use of the kidney extract. This experiment, which has been repeated by others, forms the basis of the belief that the kidney produces an internal secretion. That such a conclusion may not be warranted is suggested by the fact that the kidneys, along with some of the organs so far reviewed, are also rich in adrenal tissue—the so-called “adrenal rests” from which hypernephroma sometimes develops—and that as such they are capable, as an active factor in the immunizing functions of the body, of counteracting temporarily the toxæmia or “uræmia” brought on by removal of the kidneys. Indeed, the relief afforded is but ephemeral, death being postponed but one to two days in rabbits, in which Bitzou¹⁴⁷ repeated Brown-Séquard’s experiments. Dromain and de Pradel Bra¹⁴⁸ had also noticed that injections of kidney extract lessened the fits of epilepsy, another toxæmia. Dubois¹⁴⁹ and Renaut¹⁵⁰ have also found that kidney extracts were endowed with antitoxic power.

That we are again dealing mainly with a manifestation of the adrenal principle is further suggested by its powerful blood-pressure-raising property. Tigerstedt and Bergman found that rennin possessed this power; Bingel and Strauss¹⁵¹ recently confirmed their observation, and found that its action corresponded with that of adrenal and pituitary extracts, those of other organs causing depressor effects. The rise of pressure produced by kidney extract was high, *i.e.*, from 40 to 60 mm. Hg, and lasted from fifteen to thirty minutes. The authors concluded, moreover, that “the action of rennin, like that of adrenalin, is exerted in the muscles of the peripheral vessels.” Its general action, however, is more like that of pituitary body extract, the adrenal principle being doubtless combined organically, as in the pituitary, with bodies which prolong and perhaps control advantageously the action of the former. Like adrenal preparations kidney extract produces dilatation of the pupil. This sustains my opinion that its action is due to adrenal principle.

¹⁴⁷ Bitzou: *Jour. de physiol. et de path. génér.*, Nov. 15, 1901.

¹⁴⁸ Dromain and de Pradel Bra: *C.-r. heb. des sci. et mém. de la Soc. de Biol.*, Paris, 1895.

¹⁴⁹ Dubois: *Soc. de Biol.*, p. 287, 1903.

¹⁵⁰ Renaut: *Bull. gén. de thérap.*, T. 147, pp. 3 and 37, 1904.

¹⁵¹ Bingel and Strauss: *Deut. Archiv f. klin. Med.*, xvi, S. 476, 1909; July 26, 1895.

Even the oxidizing power I have attributed to the adrenal secretion seems to be reproduced; Batty Shaw,¹⁵² who also finds "very little justification for the existence of an internal secretion" in the kidney, remarks that "possibly nephrin and other renal preparations provide a means of stimulating oxidation in general, the kidney merely sharing in this oxidation"—a very accurate estimate from my viewpoint. Shaw adds, moreover, that "similar good results have been reported as a result of treatment by means of spermin and testicular extract," both of which, as I have shown, also owe, in all probability, their therapeutic effects to the adrenal principle they contain.

The *therapeutic application* of kidney preparations has received considerable attention, and favorable results have been reported in about one-half of the cases of chronic nephritis, or Bright's disease, in which it was tried. The mode of action, in the light of the facts submitted above, is mainly an increase of the antitoxic power of the blood and diminution, therefore, of the irritation of renal apparatus. Page and Dardelin,¹⁵³ for example, report marked amelioration in 18 cases, using a maceration prepared as follows: A very fresh kidney from a pig is cut into minute pieces, washed with fresh water to remove the excess of urine, then hashed and pounded into pulp. This pulp is put into 300 grammes (9 ounces and 5 drachms) of fresh water to which the physiological proportion of salt, 7.50 to 1000, has been added. It is then allowed to macerate for three hours, stirred occasionally, and kept in a cool place to avoid fermentation. The red water of the maceration is divided into three parts to be drunk by the patient during the day. It is more conveniently given, however, in tablet form, as "nephritin" prepared in this country by Reed and Carnrick. Only the active substance of the kidney is used in this preparation, the dose being from 10 to 15 5-grain (0.33 Gm.) tablets daily in divided doses, given between meals.

Kidney preparations have also been used with more or less advantage in puerperal intoxications and epilepsy, but their field is essentially the various forms of nephritis, and particularly for the prevention of uræmia. They also tend to increase

¹⁵² Shaw: *Loc. cit.*, p. 216.

¹⁵³ Page and Dardelin: *Presse médicale*, Dec. 21, 1904.

diuresis and reduce the albumin. As stated above, however, favorable effects are to be expected in about one-half of the cases.

MAMMARY GLAND ORGANOTHERAPY.

It is held by some that the mammary gland produces an internal secretion, but what evidence there is on the subject is so weak that it can hardly be taken into account. Introduced by Bell, of Glasgow, and in this country by the late John H. Shober, it has shown therapeutically marked stimulating action upon the uterus, but the manner in which it produces this effect has remained obscure. An extract lowers somewhat, and but temporarily, the blood-pressure and the pulse. According to Shober, it diminishes the blood supplied to the uterus and thus controls hemorrhage, its action resembling that of ergot, though free of the unpleasant effects of the latter drug. From my viewpoint, therefore, it would act by causing constriction of the arterioles.

Mammary gland is prepared in the form of a tablet made of the desiccated gland of the sheep, each tablet representing 20 grains (1.32 Gm.) of the fresh gland. The dose is from 3 to 6 tablets daily.

The *therapeutic application* is restricted to the genital apparatus. In cases of uterine fibroids characterized by excessive menorrhagia and metrorrhagia the bleeding was found by Shober to be controlled in a few weeks and the periods become regular, normal, and free from pain. There is improvement in the patient's health and weight, and the tumors themselves diminish in size up to a certain point. The patient is thus placed in a better condition for any needed operation, and often the necessity for an operation is postponed. Where there is evidence of inflammatory or degenerative changes, or when serious pressure symptoms are not controlled after a reasonable trial, operation should not be delayed. In 43 cases of uterine fibroma treated by Fedoroff, cure is claimed to have been obtained in 33, while there was a marked reduction of the growth in 43 per cent. Mammary gland is also useful in cases of subinvolution unassociated with malignancy or structural changes. Pozzi has advocated its use in uterine hemorrhage of any kind attending metritis.

Mammary gland has also been recommended to assist uterine involution and to enhance lactation. But the reports on the use of this agent have been antagonistic.

THYMUS ORGANOTHERAPY.

In the ninth chapter (p. 467), I submitted the experimental and clinical evidence which led me to suggest, in 1907, that the function of the thymus was to supply an excess of phosphorus in organic combination during the growth of the body, *i.e.*, particularly while the development of the osseous and nervous systems demanded such a reserve. This was sustained by the recognized fact that certain diseases of children and adolescents, especially marasmus, rachitis, and trophic disorders of the brain and nervous system, were due, in part, to the functions of the thymus. While it cannot be affirmed that this theory actually represents the function of the organ—the thymus having been the graveyard of many hypotheses—all that can be said for it is that it seems to account for the clinical results obtained under its use better than any hypothesis so far advanced, besides corresponding with the laboratory findings of its effects.

DISEASES OF THE THYROID.—In simple goiter it was first tried by Mikulicz,¹⁵⁴ who obtained sufficiently favorable results in 5 out of 11 cases to render operation unnecessary, at least for the time being. Reinbach¹⁵⁵ considers it probably superior to thyroid because the unpleasant effects of the latter are avoided; for the same reason it is especially suitable when organotherapy has to be used continuously. This view is based on the employment of thymus in a large number of cases in the Breslau clinic. Mikulicz gave from 2½ to 4 drachms (10 to 16 Gm.) of the raw sheep thymus on bread three times a week, increasing the dose to 7 drachms (28 Gm.) if required.

We have seen that in ophthalmic goiter it had proven efficacious in the hands of Owen¹⁵⁶ in advanced cases, and also in those of Maude¹⁵⁷ when other remedies had been used fruitlessly. The latter gave 45 grains (3 Gm.) daily to a severe case, which greatly improved, relapsing whenever the treatment was

¹⁵⁴ Mikulicz: Berlin. klin. Woch., Bd. xxxii, S. 342, 1895.

¹⁵⁵ Reinbach: Mittheil. aus den Grenzgebiet. d. Med. u. Chir., B. 1, S. 202, 1896.

¹⁵⁶ Owen: Brit. Med. Jour., Oct. 10, 1896.

¹⁵⁷ Maude: London Lancet, July 18, 1896.

interrupted. S. Solis-Cohen¹⁵⁸ also advocates its use in this disease, having found that it exerted its beneficial influence mainly upon the nervous symptoms of the disease without affecting the exophthalmus. Huston White¹⁵⁹ found that the nervous symptoms were alone improved.

These observations coincide with my own view of the manner in which thymus gland produces its beneficial effects. The excess of thyroiodase produced in exophthalmic goiter causes, we have seen, too rapid oxidation of the phosphorus in organic combination in the tissues, particularly in those of the nervous system which are extremely rich in phosphorus. Thymus, supplying phosphorus in organic combination, replaces that lost by the nervous system, thus procuring marked benefit in this one direction. As 5 grains (0.33 Gm.) of the dried thymus are equivalent to 30 grains (2 Gm.) of the fresh gland, this dose can readily be given three times daily.

RACHITIS, OR RICKETS.—The same explanation, *i.e.*, the purveying of phosphorus in organic combination—to the osseous system, in the present connection—accounts for the undoubted benefit thymus has procured in this disorder. Mendel,¹⁶⁰ having used thymus gland in 1½ to 3 drachms (6 to 12 Gm.) daily in over 100 cases, obtained marked benefit in a large proportion, but especially in the nervous symptoms, including spasm of the glottis. It had previously been tried by Stoppato,¹⁶¹ but without marked benefit. In Mendel's cases both fresh and commercial tablets were tried, the cases being subdivided as follows: 1, those which showed prodromal symptoms only; 2, those in which deformity of the osseous system was the chief feature; 3, those marked by spasm of the glottis, and, 4, those in which splenic enlargement was the most important sign. Marked improvement was noted in all after from three to four weeks, and dentition and the closure of the fontanelle proceeded satisfactorily. No untoward symptoms were noted—a marked advantage over thyroid preparations. In a case of stunted growth, obviously of osseous origin, in a boy of 14 years, R. Webb Wilcox¹⁶² ob-

¹⁵⁸ Solis-Cohen: Jour. Amer. Med. Assoc., Aug. 13, 1900.

¹⁵⁹ White: Brit. Med. Jour., vol. 1, p. 786, 1899.

¹⁶⁰ Mendel: Münch. med. Woch., Bd. xlix, S. 134, 1902.

¹⁶¹ Stoppato: Policlinico, April 15, 1897.

¹⁶² Wilcox: Boston Medical and Surgical Journal, Aug. 13, 1908.

tained $9\frac{1}{4}$ inches growth in three years by the persistent use of 2 grains (0.13 Gm.) thymus night and morning.

The view that these effects are due to the addition of phosphorus in organic combination to the body is further sustained by the results of experimental observation by Hart and Nordmann,¹⁶³ that the thymus had a definite relation to assimilation, and that it took an active part in the resistance of the organism to infection. As I will show in the second volume, page 878, nucleo-proteid, in so far as its phosphorus in organic combination is concerned, is an active participant in the immunizing process.

BRAIN AND NERVE SUBSTANCE ORGANOTHERAPY.

While these agents have given good results, the theory that brain and nerve substance possess or produce an internal secretion has never been sustained scientifically.

The clinical results, though quite discordant, particularly in the neuroses and psychoses in which these preparations have been tried, have shown a tendency to harmonize since the introduction by Sciallero¹⁶⁴ of an oily extract. Page,¹⁶⁵ who has obtained unusually good results in neurasthenia by means of injections of this extract, ascribes them to its antitoxic and antispasmodic effects. Wassermann and Takaki had previously shown that tetanus toxin was neutralized by contact with brain substance, and that when a fatal dose of tetanus toxin was injected with brain substance the fatal effects were prevented. The same observations were made in the case of hydrophobia by Babes; in strychnine and morphine poisoning by Widai and Nobécourt; in tetanus by Krokiewicz; in epilepsy by Lion and also Kaplan, using Poehl's opocerebrin—in accord with Dana's experience several years earlier. Sciallero, who obtained encouraging results in neurasthenia, hysteria, chorea, tic, and epilepsy, used his oily extract "cephalopin" in doses varying from 1 to 5 c.c. (16 to 81 minims). No untoward effects were obtained.

Although it is very improbable that brain extracts injected into the tissues act as they do in the test-tube, it seems established that they act much as do the lecithins on the market, *i.e.*,

¹⁶³ Hart and Nordmann: Berlin. klin. Woch., May 2, 1910.

¹⁶⁴ Sciallero: Riforma Medica, Jan. 27, 1904.

¹⁶⁵ Page: C.-r. de l'Académie de Méd., March 30, 1909.

by furnishing phosphorus to the organism in an assimilable form, or as nucleo-proteids in enhancing the immunizing process. Be this as it may, these substances seem to have produced effects which suggest that they are worthy of further study.

THE PINEAL GLAND ORGANOTHERAPY.

The functions of this organ have not as yet been determined to any degree. It is no longer regarded as a purely vestigial structure, however, tumors of the pineal as noted by Marburg¹⁶⁶ and others being capable of causing obesity, while Ogle, Frankl Hochwart,¹⁶⁷ and other clinicians have recorded marked precocity in young subjects, as to stature, genital development, and hair growth. These effects have also been ascribed to a secretory function, but the results obtained from extracts of the gland have been contradictory, though these agents appeared to increase the strength of the heart-beat.

A kinship with the functions pituitary is suggested by many facts. From my viewpoint, it does not possess the characteristics of a secreting gland but, seemingly, those of a nervous organ working in harmony with the pituitary body, through fibers which meet those originating from the latter organ, in the region of and in the corpora quadrigemina. The fact noted by Biedl¹⁶⁸ that in the adult animal the organ is "a negligible quantity" sustains my view, since a co-ordinating center can be sacrificed without permanent harm more readily than a secreting organ whose product should, as in the present case, deeply influence metabolism, if the effects of organic lesions of the organ are taken as standard.

As a therapeutic agent, Dana and Berkeley¹⁶⁹ claim to have obtained improvement in backward children owing to its stimulating influence on general metabolism.

HORMONE THERAPY.

The word "hormone" was applied by Starling to the group of substances secreted by various organs—the ductless glands in the group studied in this work—which could enhance the functions of other organs. Precisely as I had held three years earlier

¹⁶⁶ Marburg: *Deutsch. Zeitschr. für Nervenheilk.*, B. xxxvi, S. 112, 1908.

¹⁶⁷ Frankl Hochwart: *Ibid.*, B. xxxvii, S. 455, 1909.

¹⁶⁸ Biedl: *The Internal Secretory Organs*, p. 355, 1913.

¹⁶⁹ Dana and Berkeley: *Medical Record*, May 10, 1913.

(the adrenal secretion exciting the thyroid, the pituitary, the pancreas, etc.); these hormones were shown by Starling to reach the distant structures they influenced, through the intermediary of the blood.

While certain hormones influence various organs, others affect only one organ or a system of them. Bayliss and Starling termed "secretin" a hormone formed in the duodenal mucous membrane under the influence of hydrochloric acid from the stomach. Carried by the circulation to the intestinal mucosa, the pancreas, and the liver, it activates the production of the secretions produced by these organs. As I suggested in 1907 (see vol. ii, p. 861), this hormone presents several properties of adrenal extractives.

Another hormone has been obtained from the gastric mucosa by Zuelzer, Dohrn, and Marxer¹⁷⁰ which has been found to enhance peristalsis. It being impossible to obtain it in sufficient quantities from the stomach, it was sought elsewhere, and was found in ample quantities in the spleen—that junkshop in which red corpuscles (which, as I suggested in 1903, are the common carriers of the adrenal principle) are broken up along with other cells. This splenic hormone specifically stimulates intestinal peristalsis to a degree so remarkable that the intestinal movements in the experimental animal may be shown cinematographically ten to fifteen minutes after an intravenous injection.

This hormone (available as *hormonal* in the trade) has been found of considerable value in chronic constipation, intravenous injections (20 c.c.—5 drachms—in children and 40 c.c.—10 drachms—in adults). In intestinal paralyses following abdominal operations or volvulus it has also given satisfactory results in some cases. Henle's¹⁷¹ favorable results did not seem to be lasting. In intestinal occlusion care is necessary lest the violent peristalsis provoked aggravate any intestinal lesion that may be present. The observations of Saar¹⁷² and Unger¹⁷³ suggest, however, that the peristaltic action promoted by the hormone is not violent. The untoward effects reported by various clinicians, however, emphasize the need of great care in the use of this agent.

¹⁷⁰ Zuelzer, Dohrn, and Marxer: Berl. klin. Woch., Nu. 46, 1908.

¹⁷¹ Henle: 50th German Congress of Surgery, April, 1911.

¹⁷² Saar: Medizin. Klinik, Nu. 2, 1910.

¹⁷³ Unger: Berliner med. Woch., Nu. 11, 1911.

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